Perspective of Prevention and Tailored Diagnosis / Treatment for Breast Cancer

February 16, 2008
International Conference Hall
Aichi Cancer Center
Nagoya, Japan
The 13th Aichi Cancer Center International Symposium

Perspective of Prevention and Tailored Diagnosis/Treatment for Breast Cancer

President of Aichi Cancer Center: Yuji Nimura

Organizing Committee of the 13th Aichi Cancer Center International Symposium
Hiroji Iwata (Chairperson)
Kazuo Tajima
Yasushi Yatabe
Toshinari Yamashita
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Keitaro Matsuo
Hayao Nakanishi
Yoshiki Akatsuka
Takayasu Ishiguro
Norihiro Fujii

February 16, 2008
Aichi Cancer Center, Nagoya, Japan
PROGRAM OF SYMPOSIUM

9:00-9:05 Opening Remarks: Yuji Nimura

Review of Epidemiological Evidence and Perspective for Future Prevention

Chairperson: Chisato Nagata (Gifu University)
Hideo Tanaka (Aichi Cancer Center Research Institute)

9:05- 9:30 Keitaro Matsuo (Aichi Cancer Center Research Institute)
Epidemiologic review of breast cancer: Comparison of East and West

9:30-10:20 Susan E. Hankinson (Harvard Medical School, USA)
Perspectives on breast cancer prevention: The role of hormones

Perspective of Individualizing Pathological and Molecular Diagnosis for Breast Cancer

Chairperson: Yoshiyuki Osamura (Tokai University)
Shu Ichihara (Nagoya Medical Center)

10:20-10:35 Yasushi Yatabe (Aichi Cancer Center Hospital)
Overview of molecular classification of breast cancer

10:35-11:20 Ian O. Ellis (Nottingham City Hospital, UK)
Basal subtype of breast cancer and its clinical significance

11:20-11:55 Hitoshi Tsuda (National Defense Medical College)
Breast cancer with HER2 gene amplification

<11:55-13:00 Lunch>
**Perspective of Tailored Radiotherapy for Breast Cancer**

Chairperson: Michihide Mitsumori (Kyoto University)  
Takeshi Kodaira (Aichi Cancer Center Hospital)

13:00-13:30  
Natsuo Oya (Kumamoto University)  
A large scale analysis of single nucleotide polymorphisms associated with susceptibility to radiation dermatitis after breast radiotherapy

13:30-14:10  
Tse-Kuan Yu (MD Anderson Cancer Center, USA)  
The current status of partial breast irradiation

<14:10-14:40 Coffee Break>

**Perspective of Individualizing Medical Therapy for Breast Cancer**

Chairperson: Shinzaburou Noguchi (Osaka University)  
Noriaki Ouchi (Tohoku University)

14:40-15:15  
Jeffrey Smerage (University of Michigan, USA)  
Circulating Tumor Cells: A prognostic and predictive factor in metastatic breast cancer

15:15-15:45  
Hirotaka Iwase (Kumamoto University)  
Current status of endocrine therapy for breast cancer; optimizing by biological markers

15:45-16:00  
Hiroji Iwata (Aichi Cancer Center Hospital)  
Clinical experience and questions of anti-HER therapy

16:00-16:30  
Masakazu Toi (Kyoto University)  
Anti-HER therapy individualization

16:30-17:25  
Lajos Pusztai (MD Anderson Cancer Center, USA)  
Molecular diagnostics in the selection of therapy for early stage breast cancer-What progress have we made?

17:25-17:30  
Closing Remarks: Kazuo Tajima
Welcome Remarks

Yuji Nimura
President, Aichi Cancer Center

On behalf of the organizing committee, I am pleased to welcome you to the 13th Aichi Cancer Center International Symposium. My special thanks are to the speakers, chairpersons and participants who have traveled a long distance to join us here in Nagoya.

Our first international symposium was held in 1994 when Aichi Cancer Center celebrated its 30th anniversary and the International Conference Center was newly built. Since then the symposium has been held annually, and the organizing committee has selected timely topics on basic research, translational research, prevention, diagnosis and treatment of cancer.

The main theme of this year’s symposium is “Perspective of Prevention and Tailored Diagnosis / Treatment for Breast Cancer”. This topic was selected since considerable progress has been made in this field in recent years. The symposium consists of 4 sessions; the first session is “Review of Epidemiological Evidence and Perspective for Future Prevention”, the second is “Perspective of Individualizing Pathological and Molecular Diagnosis for Breast Cancer”, the third is “Perspective of Tailored Radiotherapy for Breast Cancer” and the fourth is “Perspective of Individualizing Medical Therapy for Breast Cancer”.

I sincerely hope that this meeting will be an excellent opportunity to learn the current status and future perspectives in breast cancer. I also wish that this symposium will contribute toward the victory a conflict with cancer all over the world.
Epidemiologic review of breast cancer: Comparison of East and West

Keitaro Matsuo
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Breast cancer is the most common cancer among women worldwide. Its age-standardized incidence rates in Japanese are 51.0 / 100,000 population (2001) and 94.8 for White in the United States (2004). Secular trend of incidence in Japan is increasing overtime. In contrast, decreasing trend is evident recently in the US. Similarly, age-standardized mortality rates are 11.4 in Japan (2004) and 23.8 in the US White (2004). Cumulative risk for breast cancer is 1.3% in Japan and 12.8% in the US White. Ethnic difference between Asians and others is evident in the US. Comparison of incidence between Japanese immigrant in the US and Japanese living in Japan showed higher incidence in Japanese immigrant. Taken these descriptive epidemiologic data, it is natural to hypothesize certain difference between genetic/environmental factors plays an important role in breast carcinogenesis.

To clarify potential risk factors for breast cancer, many of epidemiologic studies have been conducted. Currently, extensive body of evidence supported that the factors associated with endogenous and exogenous estrogen exposure are established risk factors. Moreover, several lifestyle factors are extensively examined. Recent report from World Cancer Research Fund (WCRF) classified as alcohol drinking as convincing risk factors for pre- and post-menopausal breast cancer; however, evidence is limited for Japanese. WCRF classified physical activity as probable and obesity as convincing risk factors only for post-menopausal breast cancer. Several other factors including genetic predisposition are under investigation.

In this presentation, brief overview of descriptive epidemiology and review of results from epidemiologic studies will be shown.
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Perspectives on breast cancer prevention: The role of hormones

Susan E. Hankinson
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Hormones are known to play a key role in breast cancer etiology. A number of hormones, including sex steroids, prolactin, and insulin like growth factors, have been hypothesized to influence breast cancer risk. Substantial data from epidemiologic studies support a positive association between sex steroids in postmenopausal women (particularly estrogen and testosterone), while data addressing the association with premenopausal women is limited.

A number of risk factors that are amenable to change are linked, at least in large part, to the hormonal milieu. Obesity is inversely associated with risk in premenopausal women, but is directly related to risk in postmenopausal women. Further, data are accruing that suggest weight loss in adulthood, if sustained, results in a decreased risk of breast cancer. Physical activity also is inversely associated with breast cancer risk. Alcohol intake is the best confirmed dietary factor linked to an increased risk of breast cancer. Finally, postmenopausal hormone use, particularly estrogen plus progestin use, increase risk of breast cancer in postmenopausal women. In fact, the substantial decrease in postmenopausal hormone use in the US in 2002-2003 (due to the published findings from the Women’s Health Initiative Clinical Trial) is thought to largely account for the significant decrease in breast cancer risk in 2003-2004. Overall, several ways exist to decrease breast cancer risk through lifestyle change.
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Overview of molecular classification of breast cancer

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Unsupervised hierarchical clustering in expression profiling analysis allows molecular classification of tumors, based on the similarity of genome-wide expression patterns. This new molecular-based classification shares some categories with the current pathological classification system, though it also provides additional clues to identify cancer by biological groups. Here, we overview the current understanding on the molecular classification of breast cancer.

The basic idea of molecular classification of breast cancer goes back to the first publication of an article on expression profiling analysis in 2000. In this article, four distinct subtypes were identified; the luminal cell-like subtype, the basal cell-like subtype, the HER2 subtype, and the normal breast-like cell subtype. The luminal cell-like subtype is the most common type of breast cancer, which shows positive expression of estrogen receptor (ER). Subsequent studies suggested that this subtype could be subdivided into luminal A and B, the latter of which has poor prognosis with frequent p53 mutation. The Basal cell-like subtype is characterized by high-grade morphology and negative expression of ER, PR and HER2 (triple negative). Medullary carcinoma and BRCA1-mutated cancer are always categorized into this subtype. This classification was confirmed with a population-based cohort study, and analysis using patterns of genome-wide allelic losses also supported this subtyping of breast cancer.

On the other hand, gene expression profiling analysis has also been applied directly to define gene signatures for prognostication and prediction of therapeutic response, especially in early stage breast cancer. This attempt was exemplified by a 70-gene profile associated with a poor prognosis, a recurrence score using a 21-gene signature, a wound-response signature, and a recent 186 invasiveness gene signature. Although there was also no overlapping among individual gene sets, poor and good prognosis signatures for each model were closely related with the molecular subtypes. This implied that the prognostic signatures were simply reflected in the biological profiles defined by the molecular classification. Indeed, the clinical response to chemotherapy and the recurrence rate differed among the subtypes.
A similar approach has been adopted in diffuse large cell lymphoma, brain tumors, prostatic cancer, lung cancer, and colorectal cancer. Through their analysis, new findings have been revealed that some subtypes are very different from the other subtypes even in the same organ, and are more associated with cancers of other organs.

Molecular classification definitely provides new insight to clinical oncology, shifting to a biology-based categorization of cancer.

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Basal subtype of breast cancer and its clinical significance

Ian O. Ellis
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Breast cancer is a heterogeneous group of tumors, and can be subdivided on the basis of histopathological features, genetic alterations and gene-expression profiles. One well-defined subtype of breast cancer is characterized by a lack of HER2 gene amplification and estrogen and progesterone receptor expression ('triple-negative tumors'). Identification of this group of tumors has been demonstrated to be important, because of clinical aggressiveness of this tumor type, with high risk of developing distant metastases. This triple negative phenotype has been shown to be very closely associated with the so called basal subtype of breast cancer although they are not entirely synonymous. At present there is no international consensus on the methodology or criteria to identify the basal group in clinical practice, although many markers have been proposed. Through examination of a well-characterized series of invasive breast carcinoma (1872 cases) with long-term follow-up, basal type of breast cancer can be defined based on the expression of basal cytokeratins among a panel of proposed makers. Using these criteria, the basal phenotype was associated with shorter overall survival and disease-free interval in the series as a whole and in both the lymph node (LN) negative and LN positive subgroups. When stratified by histological grade, basal type was of highly significant prognostic value in grade 3 but not in grades 1 or 2 tumours. Similarly, it was associated with poor survival in the moderate group of the Nottingham prognostic Index but not in the other groups. In a subgroup comprising LN negative grade 3 tumours, basal type was the most powerful prognostic marker followed only by tumour size, while the other variables were non-significant. Patients with basal type of cancer were more likely to respond to chemotherapy than those with non-basal tumours. Our results provide robust evidence that basal type is an important class of breast cancers with a particularly aggressive behaviour in patients particularly those with LN negative, grade 3 disease. Routine identification of basal type in breast cancer and the development of effective adjuvant treatment strategies is recommended. These are important observations as these tumours typically lack hormone receptor and HER-2 overexpression limiting the range of relevant adjuvant therapies.
Ian O. Ellis, BMedSci, BM, BS, FRCPath.

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He has been involved in the practice of pathology for over twenty five years and has an international reputation in clinical and translational research in breast disease, particularly classification of breast cancer and evaluation of prognostic factors. Author of over 300 peer reviewed scientific publications, chapters in medical textbooks and specialist textbooks in pathology and an experienced lecturer being a founder member of the faculty of the Nottingham International Breast Education Centre. He is a Fellow and a Specialty Advisor of The Royal College of Pathologists, Chairman of the UK National Co-ordinating Committee for Breast Pathology, President of the International Society of Breast Pathology, Councilor of The European Society of Mastology, Steering Committee Member of The European Group for Breast Screening Pathology and past Chairman of the Breast Pathology Working Group of the European Society of Pathology. He has acted as an advisor to the DoH, UICC, WHO and IARC. He is founder of PathLore and Medical Director of Medical Solutions plc.
Breast cancer with HER2 gene amplification

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The HER2 gene was first cloned as a proto-oncogene homologous to the HER1 (c-erbB-1, or epidermal growth factor receptor) that encodes tyrosine kinase growth factor receptor localized through cell membrane. The HER2 gene is located on chromosome arm 17q21.1, and genomic amplification of 17q12-q21.2 containing the HER2 locus occurs in 10-30% of human breast cancers. HER2 amplification causes overexpression of the HER2 protein, and plays a role in the transduction of growth signals to the nucleus.

Amplification of the HER2 gene and overexpression of its protein is correlated with histological/nuclear grade 3 and poorer prognosis of patients. It is novel situation that, at the St. Gallen International Consensus Conference 2007, HER-2 protein overexpression or HER2 gene amplification has been included in the indicators for higher-recurrence risk group of both node-metastasis-negative and positive breast cancers. Although HER2 is frequently positive in ductal carcinoma in situ (DCIS) of higher grade and with accumulation of molecular alterations, i.e., comedo-type DCIS and Paget’s disease, HER2 is not a prognostic factor in DCIS.

HER-2 tests are routinely used for the identification of metastatic breast cancer that is potentially responsive to trastuzumab (herceptin) therapy. Recently, convincing data have been published with regard to the efficacy of trastuzumab for primary systemic therapy (PST) or adjuvant therapy to operable primary breast cancer with the overexpression or amplification of HER2. A correlation between HER2 overexpression and response to adjuvant or neoadjuvant anthracycline-based chemotherapy has also been reported in many studies.

In order to measure the HER2 level, the worldwide consensus appears to be that immunohistochemistry (IHC) should be performed first and, if the results of IHC are uncertain, fluorescence in situ hybridization (FISH) should be performed later, although some investigators argue that FISH should be performed first. These tests should be performed in strict adherence to existing instructions.

Criteria for HER2 overexpression and amplification have been established. HER2 expression status, tested by IHC, is classified as score 0, 1+, 2+, or 3+. An IHC score of
3+ is judged as overexpression, or HER2-positive, a score of 0 or 1+ as negative, and a score of 2+ is equivocal, with a recommendation for retesting by FISH. Quality control is of utmost importance when performing HER-2 tests, both internal and external, for routine diagnosis and in clinical protocol studies.

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A large scale analysis of single nucleotide polymorphisms associated with susceptibility to radiation dermatitis after breast radiotherapy

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Moderate to severe acute radiation dermatitis is observed in approximately 7% of patients who receive whole breast radiotherapy. Several factors, including treatment-related, patient-oriented and genetic factors, are involved in susceptibility to severe dermatitis. The aim of the present study was to identify radiation dermatitis-related single-nucleotide polymorphisms (SNPs) using peripheral lymphocytes from patients who developed radiation dermatitis after whole breast irradiation. To elucidate genetic polymorphisms associated with a susceptibility to radiation-induced dermatitis, a large-scale, multi-institutional case-controlled study comprehensively analyzing SNPs was conducted, comparing alleles between control patients and patients with enhanced intrinsic radiosensitivity.

Patients were selected from more than 3,000 female patients with early breast cancer who received radiotherapy after undergoing breast-conserving surgery. The dermatitis group was defined as patients who developed dermatitis at an NCI-CTC grade of 2 or higher. To exclude patients with treatment-related dermatitis, patients with focal dermatitis that could be explained by comparing the dose distribution and the dermatitis distribution were strictly excluded from the present study. To determine the control group, patient-to-patient matching between the dermatitis group and the control group was employed, to ensure that the two groups would be well balanced in terms of their major characteristics and therapeutic parameters. DNA samples from each patient were subjected to the genotyping of 3,144 SNPs covering 507 genes.

SNPs that mapped to two genes, ABCA1 and IL12RB2, were associated with radiation-induced dermatitis. In the ABCA1 gene, one of these SNPs was a non-synonymous cSNP causing R219K (p = 0.006). This cSNP has been reported to be functional, suggesting that an amino acid substitution may be responsible for susceptibility to dermatitis. As for the IL12RB2 gene, a haplotype designated as H3 was
associated with dermatitis (p = 0.004). Using polymorphisms of both genes, the probability of severe dermatitis was estimated for each combination of genotypes. These analyses showed that individuals carrying a specific combination of genotypes (G homozygotes for both SNPs) accounting for 14.7% of the Japanese population have the highest probability (75%) of developing radiation-induced dermatitis. These results may serve as preliminary data for the construction of individualized radiation therapy.

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The current status of partial breast irradiation

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Long-term results from many large randomized trials have established the benefit of adjuvant whole breast radiation (WBI) following segmental mastectomy in early breast cancer patients. Meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group showed that adjuvant WBI in patient with no lymph node involvement resulted in absolute 16.1% gain in local control at 5-year, which translated into an absolute 5.1% gain in breast cancer mortality at 15-year. For patients with cancer involvement of lymph nodes, the benefit was even greater (i.e. 5-year local control gain of 30.1%, 15-year breast cancer mortality gain of 7.1%). Although increased mortality related to cardiovascular disease and secondary cancer was observed, adjuvant WBI resulted in a 15-year overall survival absolute gain of 5.3%.

Since majority of cancer recurrence in ipsilateral breast occurs near the original tumor bed, many techniques have been developed to treat only part of the breast that surrounds the tumor bed (partial breast irradiation, PBI). This would potentially reduce toxicity and result in shorter total treatment period since higher radiation dose can be delivered to a smaller volume. Fractionated PBI has been delivered through either brachytherapy techniques such as interstitial implant and balloon catheter (Mammosite) implant or multi-planar external beam technique. A single dose of intra-operative radiation has also been delivered to treat breast tissue around the tumor bed. The clinical outcomes of these treatments appear fair. The toxicity profiles of PBI are being reported. However, the interpretation of these data is hampered by their short follow-up and small sample size. Currently, an intergroup trial which compares the outcomes of breast cancer patients treated with WBI vs. PBI is accruing patients in the United States. As the data of this trial and other single arm PBI trials mature, we will find out how well PBI compares to the high standards that WBI has set.
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Circulating Tumor Cells (CTCs) - A prognostic and predictive factor in metastatic breast cancer

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Circulating tumor cells (CTCs) represent an important biologic link in the spread of breast cancer from primary to metastatic disease. CTCs are strong predictors of prognosis in patients with metastatic breast cancer. Multiple methods have been used to detect CTCs. Density gradient centrifugation, immunomagnetic capture, and size filtration methods have been used to isolate cells. Microscopy and RT-PCR have then been used to detect the isolated cells. The most reproducible methods to date have been based on immunomagnetic capture, and using these methods it appears that CTCs can be detected in 50-60% of patients with metastatic breast cancer.

The pivotal trial for CTCs in breast cancer is a prospective, double-blind, multi-center trial of 177 patients with metastatic breast cancer who were beginning a new therapy. The trial utilized independent training and validation sets. Based upon the training set, elevated CTCs were defined as ≥5 CTC per 7.5 ml of whole blood. Elevated CTCs at baseline predicted extremely short median PFS and OS of 3 months and 10 months, respectively. This is in comparison to patients with low/negative CTCs in whom PFS and OS were 7 months and 22 months, respectively. Thus baseline CTCs identify a group of high-risk patients. Even more interesting, CTC values obtained after one cycle of therapy predicted which patients were likely on ineffective therapy. Patients with elevated CTCs after one cycle of therapy had median PFS and OS of approximately 2.1 months and 8.2 months, respectively when measured from baseline. Patients who converted from high to low CTCs after one cycle of chemotherapy had a much better prognosis with median PFS and OS of 7.6 months and 14.6 months respectively. Thus it appears that patients with elevated CTCs 3-4 weeks after starting a new chemotherapy are likely on ineffective therapy. This observation has lead to the SWOG S0500 trial, in which patients with elevated CTCs 3 weeks after starting chemotherapy will be randomized to continue their current therapy versus switching immediately to a new chemotherapy. Patients on both arms will then be followed until clinical evidence of progression. Subsequent publications demonstrate that CTCs are prognostic in
patients receiving first-line chemotherapy as well as patients whose cancer has progressed on prior chemotherapy. They are prognostic in patients with bone-only disease. CTCs at 3-4 weeks also appear to predict overall survival at least as well, and possibly better than radiographic imaging performed at 3 months.

Research is now focusing on the detection of phenotypes in CTCs. Researchers have been able to detect markers such as ER, PgR, apoptosis, Bcl-2, amplification of HER2, mutations in EGFR, telomerase, mammogoblin, and others. Methods for performing gene expression arrays and multi-plex rt-PCR are also being developed.

Thus CTCs are providing a very interesting look into the biology of metastatic breast cancer. Enumeration of CTCs is currently used in the clinic to establish prognosis, and appears to detect those patients that are on ineffective therapy. Ongoing research into the detection of biologic phenotypes will hopefully lead to a better understanding of the mechanisms of metastasis, identify novel therapeutic targets, and monitor targeted therapies.

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Endocrine therapy (ET) in breast cancer represents one of the earliest molecular targeting therapies in cancer treatment. Various kinds of the ETs are currently available. To block estrogen action, selective estrogen receptor modulators (SERMs), such as Tamoxifen (TAM), Toremifene, bind to the estrogen receptor (ER), leading to attenuation of estrogen-responsive genes. The selective estrogen receptor down-regulator (SERD) antagonistically interact with the ER to completely suppress expression of estrogen-dependent genes. To block estrogen synthesis, ovarian ablation can be pharmacologically achieved by LH-RH agonist in premenopausal women. The third generation aromatase inhibitors (AIs), such as Anastrozole, Exemestane, and Letrozole, are also available for the postmenopausal women.

In adjuvant setting, 5 years TAM therapy was the standard care in the hormonal management of estrogen receptor (ER) and/or progesterone receptor (PgR) positive early breast cancer (EBC). However, recent randomized clinical trials (e.g. ATAC, BIG1-98, IES, ITA, ABCSG08/ARNO, ABCSG6a, MA-17) strongly indicate that 5-year adjuvant TAM is inadequate and that optimal adjuvant endocrine therapy for EBC should include AI either upfront or in sequence with TAM, especially in patients with high risk of recurrence. Ongoing research and clinical trials will address issues such as the long-term toxicity of AI’s, the use of AI’s in premenopausal and HER2 positive women and the choice of the best AI’s.

The need to develop and adapt better surrogate marker for adjuvant trials in EBC, will be discussed. New molecular prognostic markers and the utility of the newly approved gene profiling test will be reviewed. Other predictive markers will help to identify the patients with increased risk of relapse in order to offer them tailored targeted endocrine therapy. Additionally, target therapy to increase the sensitivity and overcome the resistance of ET will be addressed.
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Clinical experience and questions of anti-HER therapy

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It is necessary to select the treatment based on characteristics finding by targeting molecule for breast cancer patients. Especially, Anti-HER therapy is established for HER2 positive breast cancer patients. Trastuzumab (Herceptin®), a humanized monoclonal antibody targeted to the extracellular domain of HER2, benefits patients with metastatic breast cancer, and improves disease-free survival (DFS) and overall survival (OS) after adjuvant chemotherapy.

We experienced many patients with metastatic breast cancer who treated by Trastuzumab from 1992 to now. There are still many clinical questions of Anti-HER2 therapy for metastatic breast cancer patients. 1: Trastuzumab monotherapy or combination therapy with chemotherapy agents? 2: Continued or stopped Trastuzumab after cCR treated by Trastuzumab? 3: Timing of change to new drugs (for example: lapatinib)?

Initial treatment for metastatic breast cancer patients is Chemotherapy + Trastuzumab in our institution because of higher response rate rather than Trastuzumab monotherapy. However, high response rate and long duration of treatment were shown in higher HER2 gene amplification cases (more than 10 times) than standard amplification cases (more than 2 to less than 10 times) with Trastuzumab monotherapy. Furthermore, we experienced some cases obtained with cCR by Trastuzumab combination therapy. Now I still continued to Trastuzumb monotherapy for more than 3 years. Is it possible to stop the Trastuzumab treatment? We experienced also clinical trial of new Anti-HER2 therapy (lapatinib) in Japan. I will present the interesting case treated by Trastuzumab and lapatinib.

We experienced 53 patients recruited with adjuvant Trastuzumab trial (HERA study). Our disease free survival data is improved since 2002 started the HERA study because standard adjuvant chemotherapies were used for high risk patients and Trastuzumab was treated for HER2 positive patients. Now the Japanese neoadjuvant Trastuzumab randomized phase II trial (FEC100 followed by trastuzumab + weekly paclitaxel vs trastuzumab + tri-weekly Docetaxel) is ongoing for HER2 positive
patients. Furthermore, Global mega trial (ALTTO study) is ongoing in the world including Japan.

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Anti-HER therapy individualization

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It has been demonstrated that anti-HER2 therapy improves the prognosis of HER2 positive primary breast cancer patients. Forty to fifty percent risk reduction was observed either by trastuzumab monotherapy following chemotherapy or the combination with conventional chemotherapy. Current interests on the trastuzumab treatment are optimal duration of treatment, further enhancement of the treatment by other anti-HER therapies such as lapatinib and individualization of anti-HER therapy. Several major strategies for individualizing the anti-HER therapy have been proposed in recent days. Firstly, it is indicated that expressions of variant forms of HER2 that lack binding activity to trastuzumab contribute to develop the therapy resistance. Similarly, it has been pointed out that disorders in the HER-related signals such as PTEN abnormality facilitate developing resistant clones. As to immunological aspects, the relevance of ADCC and several other immune mechanisms are involved in the enhancement of the therapeutic effect, although still little has been characterized on the clinical significance. Therefore, it seems that these multiple aspects regarding the resistance mechanism or response machineries should be analyzed simultaneously and assessed comprehensively in order to precisely investigate the efficacy of anti-HER therapy in further depth.
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Molecular diagnostics in the selection of therapy for early stage breast cancer
What progress have we made?

Lajos Pusztai
U.T. M.D. Anderson Cancer Center, Houston, USA

Breast cancer is clinically heterogeneous disease and it is generally accepted that the different clinical courses of patients with histologically similar tumors is due to molecular differences among cancers. Detailed molecular analysis of the cancer therefore could yield information that may improve prognostic prediction. Recent advances in molecular analytical techniques have led to rapid expansion of potential novel diagnostics designed to personalize breast cancer care. Diagnostic companies are also increasingly adopting a clinical trial-based approach to develop their products. At least one novel genomic diagnostic test is now available in the United States to estimate the prognosis of patients with ER-positive, lymph node-negative tumors who are to receive 5-years of tamoxifen therapy. This test could help identify individuals who are at low or high risk for recurrence with endocrine therapy alone and could assist in recommending chemotherapy more appropriately for patients with ER-positive tumors. Another genomic prognostic assay (Mammaprint) was recently cleared by the FDA that may help in refining prognostic estimates for patients with node-negative tumors and could be particularly helpful for patients with stage I-II, ER-negative tumors who are undecided about adjuvant chemotherapy. This test requires fresh frozen tissue for analysis. The advent of multi-gene assays in the clinic also offers an opportunity to package multiple prognostic and predictive tests into a single diagnostic product in the not too distant future. No prospective randomized studies have been completed to demonstrate improved patient outcome with the use of any of the new tests compared with decision making based on clinical parameters only. Two such studies are currently under way, the MINDACT trial in Europe which is testing Mammaprint and the TAILORX study in the United States which is testing Oncotype DX. Survival results from these studies will not be available for several years. However, some forms of clinical benefit from these novel tests may be more subtle than improvements in survival. It may be argued that additional information that helps patients (and physicians) feel more comfortable with a particular treatment recommendation is of
value on its own.

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