Cancer Chemother Pharmacol (2005) 56 (Suppl 1): s1–s3
DOI 10.1007/s00280-005-0105-5

Yutaka Ariyoshi · Tetsuya Mitsudomi
Makoto Ogawa · Hidehiko Saito · Kaoru Shimokata
Ryuzo Ueda

Preface

Published online: 5 November 2005

For the 20th Bristol-Myers Squibb (BMS) Nagoya International Cancer Treatment Symposium, the organizers and sponsor of this annual event decided to look at the current status and future perspectives of hormone-related cancer under the theme ''New Concepts of Treatment Strategies for Hormone-Related Cancer''. As in the previous meetings, this special occasion was marked by the presence of respected international and local speakers and numerous attendees.

This annual event aims to promote free discussion among participants and speakers. More than 400 physicians and scientists from around the world attended the 2005 Symposium and listened to 14 speakers who discussed the basic and clinical aspects of hormone treatment for breast cancer and prostate cancer. The attendees were also able to take part in the ''Meet the Expert'' sessions; informal discussions with three of the international invited speakers, to allow participants to present their ideas and gain new perspectives, in a casual small group setting.

The meeting began with the Presidential Opening Address by Hidehiko Saito (National Hospital Organization, Nagoya Medical Center, Japan). He pointed out that the past 20 years have seen remarkable changes in cancer chemotherapy and that the meeting is an excellent opportunity to grasp current status and future perspectives of hormone-related cancer.

The first keynote address entitled ''Function of nuclear sex hormone receptors in gene regulation'' was given by Shigeaki Kato (Institute of Molecular and Cellular Biosciences, University of Tokyo, Japan). Sex steroids exhibit a wide variety of biological actions in physiological and pathological events. Development of reproductive organ tumors such as breast and prostate cancer often depends on the action of sex hormones, but the molecular basis remains totally unknown. Dr. Kato talked about the function of nuclear receptor in gene regulation, crosstalk of estrogen receptor (ER) α-mediated estrogen signaling with growth factor and dioxin signaling, and the role of the h androgen receptor (hAR) mutant in prostate development. He concluded that hypersensitivity of AR mutants to antagonists and endogenous steroid hormones might potentiate hormone-dependency in prostate cancer development.

Rachel Schiff (Breast Center, Baylor College of Medicine, Houston) delivered the second keynote address, which focused on advanced concepts in ER biology and breast cancer resistance. New research has highlighted the role of both genomic and non-genomic ER activities and their intimate molecular crosstalk with growth factor receptor and other signaling kinase pathways in endocrine resistance, and this was discussed by Dr. Schiff. These signaling pathways, when overexpressed and/or hyperactivated, can modulate both activities of ER, resulting in endocrine resistance. These signal transduction receptors and signaling molecules may therefore serve as both predictive markers and novel therapeutic targets to circumvent endocrine resistance. Data from preclinical studies of treatment combinations with various endocrine therapy drugs together with several potent anti EGFR/HER2 inhibitors are very promising, and the clinical trials are now underway to see if this new strategy is effective in patients.

In commemoration of the meeting's 20th anniversary, BMS created a special award given to young researchers who bring about a notable advance in the field of cancer treatment in the twenty-first Century. The first recipient was Shigehira Saji (Tokyo Metropolitan Komagome Hospital, Japan). The subject of his 2005 BMS Award lecture was the clinical significance of ERβ in breast cancer and he talked about the function, expression and future perspectives of ERβ. Epidemiological studies of hormone replacement therapy and isoflavone (genistein)

H. Saito (✉)
National Hospital Organization, Nagoya Medical Center,
Sannomaru 4-1-1, Naka-ku, Nagoya 460–0001, Japan
E-mail: Saitohi@nnh.hosp.go.jp
Tel.: +81-52-9511111
Fax: +81-52-9510559

consumption have indicated the possible contribution of ERβ-specific signaling in breast cancer prevention. Dr. Saji postulates that a selective estrogen receptor modulator, which works as an antagonist of ERα and an agonist of ERβ, may be a promising chemopreventive treatment.

The title of the first session was "Gene Tip, Prognosis factor, SNP". Prediction of individual responses to hormonal therapies for breast cancer, including selective estrogen receptor modulators (SERMS) and aromatase inhibitors, prior to start of treatment has recently gained much importance. Shin-ichi Hayashi (Tohoku University, Japan) began the session by talking about the tools that his group is developing, such as focused microarray and GFP-reporter cells systems, to address basic and clinical issues. A focused microarray of limited numbers of genes has many advantages for specific studies of estrogen signaling. Following previous work by his group, Dr. Hayashi is developing a custom-made microarray system made up of the selected genes and attempting to apply them to research on breast cancer. Although further study is required, he believes that this technique and other related methods will provide new insights in the elucidation of estrogen-dependent growth mechanism of cancer, as well as the clinical benefits to patients by assessment of other individual responses to endocrine therapy.

The second session was entitled "Hormone Treatment (including aromatase inhibitor)". The use of aromatase inhibitors in adjuvant therapy for early breast cancer (EBC) was the topic of the talk given by Walter Jonat (University of Kiel, Germany). Clinical evidence supporting the use of aromatase inhibitors (AIs) in adjuvant therapy for hormone-sensitive EBC has grown rapidly over the past few years. Unlike tamoxifen, which inhibits the estrogen receptor pathway and transcription of estrogen-regulated genes, AIs prevent synthesis of estrogen by inhibiting the aromatase enzyme that catalyses the conversion of androgens to estrogens. Clinical development has led to the availability of three third-generation AIs: anastrozole and letrozole (both non-steroidal AIs) and exemestane (a steroidal AI). The outcomes of recent clinical trials and their implications for clinical practice were presented by Dr. Jonat.

Findings suggest that there are numerous steps and complicated mechanisms responsible for endocrine resistance. Novel strategies modifying these steps may retard the development of endocrine resistance and/or overcome endocrine resistance. Junichi Kurebayashi (Kawasaki Medical School, Japan) reviewed the molecular mechanisms responsible for endocrine resistance in breast cancer, such as reduction in or loss of ER expression, dysfunction of ER signaling, and ligand-independent activation of ER. He also spoke about the possible therapeutic strategies against this resistance, including inhibition of the growth factor signaling pathway and retardation of the development of acquired endocrine resistance. Dr. Kurebayashi pointed out that clinical researchers have to make a continuous effort to develop new strategies for enhancing or prolonging the efficacy of endocrine therapy.

"Hormone Treatment for Prostate Cancer" was the title of the Symposium's third session. It began with Martin E. Gleave (Vancouver General Hospital, Canada) who talked about therapeutic strategies aimed at delaying progression of late-stage prostate cancer to its lethal state of androgen independence. More than 80% of men with advanced prostate cancer have symptomatic and objective responses following androgen suppression, and serum prostate-specific antigen levels decrease in almost all patients. Dr. Gleave addressed the optimal timing of hormone therapy, the current status of intermittent androgen suppression, and the future biologic agents targeting the molecular basis of hormone resistance. He also discussed the rational and progress regarding targeted therapies to enhance tumor cell death after androgen withdrawal or taxane chemotherapy.

Current issues and future directions in hormone treatment for prostate cancer was the subject of the presentation given by Tomohiko Ichikawa (Chiba University, Japan). He reported on the two mechanisms of androgen-refractory prostate cancer, i.e. the androgen-refractory-dependant pathway and the androgen-refractory-independent pathway, and their possible treatment strategies. Dr. Ichikawa ended by saying that although numerous molecular prostate cancer studies have been performed, the mechanism by which prostate cancer cells survive after androgen-ablation therapy is still a mystery. When more cell-survival pathways are defined, it is possible that improvement of survival for patients can be achieved by developing specific gene-targeting therapies to interfere with these pathways.

The special lecture was given by Michael F. Clarke (University of Michigan Medical School, Ann Arbor). It is well known that cancer cell lines provide invaluable information. However, their biological properties can often differ in crucial ways from de novo cancer cells. Dr. Clarke presented findings of his group from a self-renewal assay for cancer stem cells. Their novel mouse model reliably permits the isolation of individual cancer cells directly from patients' tumors for assay. In his opinion this will allow the characterization of crucial signaling pathways involved in processes critical for tumor formation by cancer cells within de novo tumors. Targeting abnormal self-renewal pathways in cancer cells may result in more effective cancer therapies.

The closing session focused on "Chemotherapy: (including new drugs)". Maha Hussain (University of Michigan Comprehensive Cancer Center, Ann Arbor) began this session with a presentation on chemotherapy for prostate cancer. She focused on the implementation of early systemic therapy to improving outcomes, reviewing the findings of several trials and investigations that looked at clinically localized prostate cancer, adjuvant chemotherapy and neoadjuvant chemotherapy. Dr. Hussain believes that improvements in systemic therapy for prostate cancer over the past 10 years have opened the way for the active investigation of new and

effective treatments in all stages of the disease. Defeating prostate cancer will require a solid commitment to continued clinical/translational research in this area, with all appropriate patients being offered access to clinical trials.

The next talk was delivered by Andrew D. Seidman (Memorial Sloan-Kettering Cancer Center, New York). He began by outlining the theoretical framework for dose-dense chemotherapy in breast cancer. Dr. Seidman then went on to review recent clinical trials that address this concept and approach to breast cancer treatment. After many years of pilot feasibility studies of dose-dense chemotherapy regimens, there are now phase III data that show the advances of this approach in the adjuvant treatment of breast cancer. Dr. Seidman concluded that 'A new chapter has begun, one that seems to hold greater promise than the chapter of dose-intensity in breast cancer. Ultimately, both the discovery of new agents and clarification of optimal scheduling and dosing must serve the interests of patients with breast cancer maximally'.

In his presentation, Toshiaki Saeki (Saitama Medical School, Japan) focused on drug resistance in chemotherapy for breast cancer. He summarized the most recent preclinical and clinical data of dofequidar, and the rationale for toremifene and paclitaxel combination chemoendocrine therapy for breast cancer. Dr. Saeki discussed the role of P-gp protein in breast cancer, and how its expression in tumours may be linked to certain clinical drug resistance. P-gp may be an important target to improve the efficacy of chemotherapy. Antiestrogens could also moderate P-gp-related resistance in vitro. Indeed, toremifene has demonstrated a synergistic effect in combination with paclitaxel on various human breast cancer cell lines. In the clinical setting, combination chemoendocrine therapy of paclitaxel and toremifene may be an attractive strategy for the treatment of breast cancer.

Kazuto Nishio (National Cancer Center Research Institute, Japan) talked about translational studies for target-based drugs. He outlined the correlative studies taking place at the National Cancer Center Hospital such as those involving gene expression profiles, a toxicogenomic project for breast cancer, biomarker monitoring for tyrosine kinase inhibitors and proteomics technology.

Trastuzumab, a humanized anti-Her-2 monoclonal antibody was the topic of the overview given by Masakazu Toi (Komagome Hospital, Japan). Trastuzumab has had an enormous impact on clinical management of breast cancer: survival of Her-2 positive metastatic breast cancer patients has improved significantly, and tumor Her-2 status has been built into the decision-making tree for primary breast cancer patients. Dr. Toi summarized the recent improvements of survival resulting from trastuzumab-based therapy in Her-2-positive metastatic breast cancer patients and several translational research aspects for future anti-Her-2 therapy.

We would like to express our gratitude to all the participants in the 20th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium. We also thank Bristol-Myers Squibb for their continuing generous support for this symposium series, which has made it possible for us to celebrate this extraordinary event.