Dear Colleagues,

It is with great pleasure that the Organisation for Oncology and Translational Research (OOTR) welcomes you to our 9th Annual Conference, held for the first time in Bangkok, Thailand from March 22-24, 2013. We are delighted that this year’s event establishes a new partnership in which the OOTR annual meeting will run as a conjoint conference with the Fifth Asian Oncology Summit (AOS). This coming together of our two organisations underscores the increasing and necessary blurring of barriers between what classifies as translational oncology and what is clinical research and practice-shaping medicine. The synergies between the aims of the AOS and the OOTR are palpable and we hope we have created a diverse and stimulating programme with a wide range of interests for all attendees. We are particularly delighted to have such a distinguished faculty this year, many of whom have been pioneers in their fields. We hope you find time to attend as many sessions as possible so our speakers receive a warm welcome. Please feel free to talk to faculty at any time: this is one of the best aspects of the AOS—the size of the event and relaxed atmosphere make it a convivial meeting to network, establish new collaborations and friendships, or simply catch-up with old acquaintances and colleagues.

Warm regards,

Louis Chow
Chair, 9th Conference of OOTR
Executive Director, OOTR

Masakazu Toi
Chair, 9th Conference of OOTR
President, OOTR

Rob Brierley
Chair, AOS 2013
Deputy Editor
The Lancet Oncology

Preface

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Editorial

Triple Negative Breast Cancer, how to select the right chemotherapy for the right patient?

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Triple-negative breast cancer (TNBC) is a name commonly used for a group of breast tumors characterized by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 (HER-2) expression measured by immunohistochemistry and/or fluorescence in situ hybridization. Patients with TNBC Metastatic Breast Cancer (MBC) have poor prognosis with a median of overall survival of approximate 9 - 13.3 months (1-4). The treatment options are mainly limited to cytotoxic chemotherapy (5, 6). Interestingly, it is recognized that a subset of patients with TNBC respond better to chemotherapy (1, 7). BRCA and p53 gene mutations highlight the possible sensitivity cytotoxic agents (8) including taxanes, anthracycline- or platinum salt-based chemotherapy. Although it is well noted for sensitivity of BRCA-mutated breast cancer to platinum compounds, definitive conclusion on the use of best chemotherapy for TNBC patients is difficult considering the incomplete overlap of BRCA-mutated breast cancer and TNBC. For patients with early TNBC, anthracyclines and/or taxanes in the neoadjuvant setting seems to be a good choice (9).

In the metastatic setting, rapid progression of the disease is commonly observed given that many tumors show resistance to anthracycline and taxanes after treatment in the neo-adjuvant setting and other treatment options provide minimal benefit. Other non-cross-resistant chemotherapeutic agents such as nab-Paclitaxel, gemcitabine, bevacizumab, vinorelbine could be considered, but single agent chemotherapy does not improve survival at all. Instead, combination chemotherapy might help (10, 11). Targeting the tumors angiogenesis has been considered as a possible treatment strategy for TNBC. However, in the...

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E2100, AVADO and RIBBON-1 trials, the addition of bevacizumab did not demonstrate an improvement in overall survival (12-14). Definitely, prolongation of overall survival is of utmost importance for MBC patients.

Despite the negative results in large randomized clinical studies, the question if targeting the angiogenesis in metastatic TNBC (mTNBC) could prolong OS in a subset of patients remains unanswered. We previously reported a case of primary metastatic TNBC (mTNBC) with lymph node, lung and bone metastases (10). The patient was treated with systemic chemotherapy (gemcitabine 1,500 mg/m², nab-paclitaxel 150 mg/m², and bevacizumab 10 mg/kg once every other week). A complete radiologic response was achieved after 7 months of the treatment and the progression-free and overall survival were 3 and 5 years respectively. The triplet chemotherapy was effective and the patient experienced minimal side effects. This case may indicate that adding antiangiogenic therapy to chemotherapy may warrant further investigation on the effectiveness of different regimens. An in-depth examination on how and why patient could benefit from the therapy is necessary.

Differential responses to the costly treatment have indeed driven the development of predictive biomarkers. Several markers such as circulating VEGF-A protein, VEGF isoforms, VEGFR gene polymorphisms, deta-like ligand 4 as well as neuropilin-1 were identified as possible predictive markers for bevacizumab outcomes (15-18). However, it is still not the right time to employ these predictive markers into the clinic owing to the inconsistency of the results. In addition, the complexity of mechanism of angiogenic pathway and the changing biologic mechanism during antiangiogenic therapy further complicate the clinical application. However, it is obvious some patients benefit from the combination of antiangiogenic therapy and chemotherapy with the prolongation of progression-free survival. Certainly, TNBC patient should be further sub-classified by molecular profiling in order to identify which patient will benefit from what therapy. In a recent study, neoadjuvant use of cisplatin seems effective a subset of TNBC with lower BRCA1 mRNA expression (7), which might further highlight the homogeneity among TNBC with BRAC1 mutation. However, this is not the case for carboplatin. Therefore, the future will be about the identification of subsets of patients among TNBC and translational research will be the key to finding the right treatment options.

References:

OOTR Initiatives

OOTR Educational Seminar and Investigators Meeting
At 8:00 AM Professor Sasano of the Department of Pathology, Tohoku University School of Medicine in Japan gave his lecture “Pitfalls of translational research in oncology – Potential discrepancies between bed and benchsides”.

Recent progress in basic science resulted in a marked contribution to the management of the cancer patients as well as to the development of novel treatment. This is primarily due to the progress of translational research, which applies the results of basic science to solving the clinical problems oncologists face every day.

Although the Educational Session was open to all delegates of the joint conference, in particular young doctors and researchers were given an opportunity for participation, and some were provided with a grant from OOTR to attend the seminar.

After the successful educational seminar, Dr. Louis Chow, Honorary Clinical Professor of The University of Hong Kong and Executive Director of OOTR, welcomed investigators from Asia and Europe to the Investigators Meeting. Following the sharing of the most recent publication on the final results of the N001 study in Expert Opinion on Investigational Drugs, Dr. Chow, together with Professor Masakazu Toi of Kyoto University and President of OOTR introduced several new study proposals. The participants were asked to comment on the feasibility of these new studies.

Alongside evaluating new clinical trials, the group also discussed current ongoing studies. Professor Toi presented the results of the OOTR-N003 study, a randomized trial of docetaxel with or without capcitabine as neoadjuvant chemotherapy in female patients with operable breast cancer who did not experience disease progression after 4 cycles of 5-Fluorouracil, epirubicin and cyclosphamide. A total of 500 subjects were recruited in this study, and a biomarker evaluation is being planned.

Dr. Chow then provided updates of two ongoing studies: OOTR-N006 and N007. OOTR-N006, a randomized study of mTOR inhibition by RAD001 (Everolimus) in invasive breast cancer patients after pre-operative use of anthracycline and/or taxane based chemotherapy is currently recruiting subjects at sites in Korea and in Hong Kong. The recruitment status, interim results on efficacy and toxicity were discussed with the group.

The recently initiated OOTR-N007 study is a Phase II neoadjuvant study of letrozole in combination with PD-0332991 (oral CDK4/6 inhibitor) for ER positive, HER2 negative breast cancer in postmenopausal women, currently open at two sites. Besides the study design and the outcomes in the first few patients treated with the combination therapy, Dr. Chow also presented data from SABCS 2012 on a global phase II study of letrozole plus PD-0332991 in patients with ER positive metastatic disease. Shortly afterwards, the meeting was adjourned.
On Saturday, March 23, 2013 Professor Hironobu Sasano, Director of Department of Pathology, Tohoku University School of Medicine will deliver a lecture in the Translational Oncology session entitled:

“Biomarkers of cell proliferation: how to evaluate the status of cell proliferation in human malignancies”.

With an increasing understanding of the tumor biology, numerous biomarkers have been explored for disease staging, treatment response prediction and prognostic determination. There are a lot of prognostic models for recurrence risk assessments, but not all of them are widely used. It is of utmost importance to identify objective parameters related to clinical outcomes from the surgical specimen. Cell proliferation of carcinoma cells is the objective parameter (1-6). Presently, there are no existent biomarkers in serum and/or urine to provide the information for the status of cell proliferation in cancer patients. Prof. Sasano said, “Considering the reasonable scientific accuracy and practicality, labeling index based on Ki67 immunohistochemistry using MIB1 monoclonal is the most widely available and accurate marker of providing information as to the proliferative activity of tumor cells.”

Cut-off values of proliferative markers are always an issue. Prof. Sasano commented on the challenges to the clinical applications of biomarkers: “This is the problem which has not been solved yet. You must go back to the principles as to why you performed the analysis of cell proliferation in tumor cells in the cancer patients. Any cut-off values should be based on the clinical utility such as prognosis of the patients, response to specific treatment and others. This means that each cut off point may be different in individual situations, such as the response to specific therapies or prognosis of the patients.” Regarding the use of Ki67 as a predictive or prognostic marker, or both, Prof. Sasano said, “This [Ki67] can be used in both points but reproducibility, especially among different institutions or even pathologists, is cardinal to apply this method to the marks of both fields.”

In regard to best use the biomarkers in the clinic, Prof. Sasano said, “Similar to the agenda above, it is about clinical relevance and wide availability. This means that the technique for determination of the biomarkers should be able to be performed without that much difficulty in credited or reputable diagnostic laboratories and not necessarily in the settings of research or academic laboratories.” Speaking about the use of biomarkers for cell proliferation in his future research, Prof. Sasano added, “Further refinement of automatic analysis following the screening of the pathologist in the slides is needed. However, the differentiation from non-malignant cells could pose serious problems in this regard.”

Prof. Sasano will share with us more on the important factors for managing early breast cancer with the biomarkers and discuss about the factors which will influence the interpretation of Ki67 labeling index in his lecture.

References:

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The mTOR pathway first sparked interest as a potential anti-cancer drug target in the 1990s when researchers identified the yeast and mammalian targets of rapamycin (sirolimus). Rapamycin is a macrolide produced by Streptomyces hygroscopicus, which was isolated in 1975 during antibiotic screening of soil from Easter Island in Pacific Ocean. Besides being a potent fungicide, rapamycin has broad antiproliferative effects and was developed as an immunosuppressant, which is used to prevent chronic kidney transplant rejection. Despite rapamycin’s impressive and tantalizing anti-neoplastic properties in vitro, clinical development as an anti-cancer agent was not vigorously pursued due to its aqueous insolubility and unstable pharmachemistry. Consequent work to synthesize pharmacologically superior analogs, such as everolimus (Afinitor®; Novartis Pharmaceuticals), has since reignited enthusiasm for the role of mTOR inhibition in cancer.

Rapamycin binds to FK506 binding protein 12 (FKBP12), which is the major receptor that mediates immunosuppression by rapamycin, cyclosporin A and FK506. The principal downstream target of the FKBP12-rapamycin complex is mTOR which is a serine/threonine kinase ‘master regulator’ that integrates complex internal and external signalling pathways. Although the functions of mTOR remain incompletely understood, it is known to modulate processes critical to cell growth and division, as well as responses to DNA damage and nutrient deprivation. Several concurrent investigations revealed the pivotal role of mTOR in cell growth and proliferation. A working model demonstrated that dysregulated upstream signals in cancer cells, such as growth factors receptors, PI3K, TSC gene and PTEN, etc, hyperactivated mTOR resulting in uncontrolled cell growth. Conversely, FKBP12-rapamycin complex inhibits mTOR-stimulated expression of proteins involved in oncogenesis, in particular, tumor progression, cell growth and proliferation, cellular bioenergetics, and tumor angiogenesis.

Everolimus is a highly specific inhibitor of the mTOR serine/threonine kinase complex. It has demonstrated continuous inhibition of mTOR and its downstream targets 4E-BP1 and S6K1 in cell lines, and also demonstrated in vitro inhibition of proliferation of cancer cell lines across multiple tumor types with a broad range of activity. In order to ensure continuous inhibition of the mTOR pathway, the current development program and approved indications with everolimus are based on the once daily schedule. Clinical signals have been observed with everolimus across multiple tumor types, including BC, RCC, TSC, HCC, neuroendocrine tumors, gastric cancer, lymphoma, adenocystic carcinoma, melanoma, and mesothelioma. More recently, in the pivotal BOLERO-2 phase III trial, the combination of everolimus with exemestane showed significant improvement in efficacy, in terms of PFS, response rate, and clinical benefit rate, relative to exemestane monotherapy in postmenopausal women with ER+ advanced BC previously treated with aromatase inhibitors (Baselga, 2011, Hortobagyi 2011, Piccart 2012). PFS by local assessment was 7.8 months for everolimus + exemestane vs 3.2 months for exemestane + placebo (HR 0.45; 95% CI 0.38–0.54; P<0.0001). Overall response rate (12.6% vs 1.7%; P<0.0001) and clinical benefit rate (51.3% vs 26.4%; P<0.0001) were superior in the everolimus + exemestane arm vs exemestane + placebo. Analyses by central assessment showed a median PFS of 11.0 months with the combination vs 4.1 months with the monotherapy (HR 0.38; 95% CI 0.31–0.48; P<0.0001), confirming the results of the primary PFS analysis.

OOTR is currently conducting the OOTR-N006 study: a randomized study of mTOR inhibition by RAD001 (Everolimus) in invasive breast cancer patients after pre-operative use of anthracycline and/or taxane based chemotherapy (NCT 01088893).