Friday, 18 April 2008 08:00–08:45

EUROPA DONNA TEACHING LECTURE

Biology, not chronology, driven treatment

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Biology, not chronology, driven treatment of breast cancer in the elderly

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As age advances, patients will suffer both from ailments related to senescence and to cancer. Many will need the expertise of the geriatrician and of the oncologist who will participate in specific "case-discussions" to look at social and medical issues that will affect the treatment plan (with surgery, radiation and drug therapy, rehabilitation, supportive and palliative care questions often intertwined). Patient desires are a key in this discussion, taking into account the variable reality of family or community support, which is so different among the many cultures and their present changes in a world which moves very fast, faster than most elderly (and not so elderly) people can apprehend. The International Society of Geriatric Oncology has created a task force to assess the available evidence on breast cancer in elderly individuals, and to provide evidence-based recommendations for the diagnosis and treatment of breast cancer in such individuals. A review of the published work was done with the results of a search on Medline for English-language articles published between 1990 and 2007 and of abstracts from key international conferences.

Recommendations on the topics of screening, surgery, radiotherapy, (neo)adjuvant hormone treatment and chemotherapy, and metastatic disease will be summarized during this lecture. Oncologists are now learning to take into account the physiologic age of their patient, which is the reflection of a normal and sometimes abnormally accelerated loss of body reserves, certainly related to chronological age but not precisely dictated by this one. Understanding the biology of breast cancer will allow one to optimally adapt the treatment of the elderly patient, considering that cancer treatments should not be synonymous of undue hardship imposed on the patient who would anyway die from another competing cause of mortality. But biases prevail also, and as an example let us cite that while adjuvant breast cancer chemotherapy is yet to be accepted and codified in the elderly, one assists to a remarkable exercise of schizophrenic thinking about chemotherapy, where lymphoma experts feel that anthracyclines are part of curative treatment in the elderly and breast cancer experts debate about the potential for cardiac insufficiency related to these drugs. Treatment proposals should be made on the basis of objective evidence, based reasoning, and the subjective and sometimes highly emotional discussions are understandably part of the patient's reactions.

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Friday, 18 April 2008 09:00–10:30

KEYNOTE SYMPOSIUM

Challenges in breast cancer molecular targeting

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Systems biology approach to the discovery and implementation of targeted therapeutics

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The realization of the promise of personalized molecular medicine will require the efficient development and implementation of novel targeted therapeutics. The goal will be to deliver the right drug to the right patient at the right time at the right dose. This effort will require a integration of information from the DNA, RNA and protein level into predictors of which patients are likely to respond to particular therapies. The overall likelihood of response to particular drugs represents the interaction between predictors of sensitivity with predictors of resistance. Efficient clinical trials testing these precepts will require the development and implementation of novel trial designs. It is likely that we will need to increase the size of phase I and II trials to allow the identification and validation of molecular markers at the same time as the initial evaluation the toxicity and efficacy of targeted therapeutics. This will come with the advantage of being able to deliver targeted therapeutics to enroll a much smaller population of patients selected for the likelihood to respond in phase III trials accelerating the approval of effective targeted therapeutics.

The phosphatidylinositol 3′kinase (PI3K) pathway is aberrant at multiple levels across a wide variety of tumors making it the most common activating aberration in cancer. This has led to the development and now early clinical testing of drugs targeting multiple components of the pathway. The efficient utilization of these drugs will require the ability to accurately determine mutation and activation status in tumors as well as determining the interaction between the PI3K pathway and other pathways in driving tumor pathophysiology. Using a novel accurate and sensitive mass spectroscopy based sequencing approach, we have evaluated mutations in the PI3K pathway across more than 500 breast cancer samples. We have also implemented a high throughput functional proteomics approach designated reverse phase protein arrays to characterize the level and activity of multiple signaling pathways. We demonstrate than an integrated analysis of mutation, proteins levels and protein activity is able to predict lack of response to trastuzumab in patients and to novel drugs targeting the PI3K pathway in vitro. This demonstrates that the response to targeted therapeutics is due to an interaction of markers of sensitivity and markers of resistance and provides important approaches for patient selection.

The PI3K pathway is critically important to cellular function and is thus under exquisite homeostatic control. The feedforward and feedback loops in the pathway determine the response to perturbation of the pathway by mutation or therapeutic intervention. Strikingly inhibition of the pathway at the level of mTOR or AKT results in the activation of potent feedback loops resulting in activation of multiple cell surface tyrosine kinases, PI3K itself and in the case of mTOR inhibitors, AKT. This may contribute to the observation that mTOR inhibitors appear to make some patient tumors grow more rapidly an unexpected and disappointing consequence of targeted therapeutics. Our preliminary systems biology-based mathematical and experimental models of the PI3K signaling network accurately predict these consequences as well as the biochemical processes involved. Further, the models suggest combinations of targeted therapeutics likely to reverse the negative effects of the mTOR inhibitors converting the outcome from negative to positive in terms of tumor growth.

Systems biology is the study of the emergence of functional properties that are present in a biological system but that are not obvious from a study of its individual components. Systems biology is a data-driven process requiring comprehensive databases at the DNA, RNA, and protein level to integrate systems biology with cancer biology. Combining these patient and model-based databases with the ability to interrogate functional networks by a systematic analysis using siRNA libraries and chemical genomics provides an ability to link in silico modeling, computational biology, and interventional approaches to develop robust predictive models applicable to patient management.