Monday, 24 September 2007

Opening session (Mon, 24 Sep, 09:00−10:30)

1 INVITED

Translating basic research into patient benefit: The druggable cancer genome

P. Workman. *The Institute of Cancer Research, CRUK Centre for Cancer Therapeutics, Sutton, United Kingdom*

The progressive unravelling of the mysteries of the cancer genome, and in particular the identification of the mutations and epigenetic abnormalities that drive the malignant phenotype, provides previously unprecedented opportunities for basic and translational research. One of the key areas in which our knowledge of the cancer genome and resultant hijacked signal transduction pathways is being best exploited is targeted drug development. Although drug discovery remains technically challenging, it is increasingly possible to develop molecular therapeutics that act on deregulated cancer gene products. Progress has been particularly impressive in the development of drugs, both antibodies and small molecules, acting on kinases. Many kinase inhibitors are highly selective whereas others showed a broader pattern of activity. Given that most cancers are likely to be driven by several molecular abnormalities, and also recognising that the development of drug resistance clearly remains a major problem even with the new molecular therapeutics, it can be argued that optimal therapy will require combinatorial therapeutic approaches. These can be designed rationally to attack multiple points of intervention, either on the same target, at different points on the same oncogenic pathway, or on distinct pathways. They can also be selected to attack different biological effects or hallmark traits of cancer. In addition to carefully constructed cocktails of highly selective molecular therapeutics, drugs that act on multiple molecular targets, or on multiple therapeutic targets downstream of a single but broadly influential target, offer alternative therapeutic options. Examples of the latter include the molecular chaperone HSP90, the proteasome or chromatin modifying enzymes such as histone deacetylases. In addition, combinations of molecular therapeutics with cytotoxic agents will also find utility. Strategic and technical approaches to drugging the cancer genome will be illustrated by our work the discovery of inhibitors against targets such as HSP90, PI3 kinase, AKT/PKB, CDKs, B-RAF and chromatin modifying enzymes. The focus of the talk will be on the overcoming the current challenges by integrating new approaches to targets, technologies and treatments. Particular emphasis will be placed on molecular biomarkers as we move towards the vision of personalized molecular cancer medicine.

Supported by Cancer Research UK

2 INVITED

Moving cancer treatment into the 21st century

M. Piccart. *Institute Jules Bordet, Medicine Department, Brussels, Belgium*

Introduction: Exploiting the great knowledge acquired in the 20th century about cancer genes to develop both molecular biomarkers and molecular therapeutics forms the basis for the development of personalized cancer medicine in the 21st century.

In simple words, finding the right treatment for the right patient at the right time is the greatest challenge oncologists are facing nowadays.

We will take the example of early breast cancer (BC) therapy to illustrate the most striking clinical advances already accomplished as well as future directions for clinical and translational research.

Selection of adjuvant systemic therapies: historical perspective: Our oldest adjuvant treatment modalities – chemotherapy and tamoxifen – have first been evaluated in "high risk" patients, namely those harbouring large tumors with nodal involvement, without too much attention paid to the biological features of the primary tumor.

The definitive proof of their benefit to women with early breast cancer was brought by the Overview in the 1980's. An important progress was accomplished when the tamoxifen Overview data were dissected according to estrogen receptor (ER) status: while ER "rich" tumors derived an important benefit from tamoxifen, this benefit was virtually inexistent in ER "poor" tumors. A first window into the world of "targeted" therapies had been opened . . .

The IBCSG investigators were the first to attempt a "dissection" of the chemotherapy effects and to show marked heterogeneity in the magnitude of chemotherapy benefit between ER "absent" tumors and ER "rich" tumors, with the former showing much enhanced benefit. These observations were based on retrospective, exploratory analyses, done first in the context of IBCSG clinical trials and later in the context of the Overview. The latter, however, failed to isolate a subset with "no benefit" and suffers, in addition, from the pooling of a large variety of chemotherapy regimens, some of which are no longer in use today. As a result, the majority of oncologists continue to prescribe chemotherapy with "risk" as the target!

Trastuzumab had a much easier "route" to the field of tailored adjuvant therapies: from the start, its testing was restricted to the right population, namely women with HER2 overexpressed / amplified tumors, a factor that has undoubtedly contributed to its success.

The St-Gallen 2005 meeting introduced a fundamental change in the treatment allocation paradigm: "first select the target in the tumor . . . then think about risk, using the latter to assess trade-off between anticipated efficacy and toxicity". We will propose that this paradigm is the corner-stone of modern "tailored" adjuvant therapy. While recent progress has been done in evaluating "risk", much work still needs to be done in identifying the Achilles' heel of each tumor for therapy selection.

Multi-gene prognostic signatures on their way to the clinic: Fairly reliable gene-expression signatures predicting BC outcome have been developed in the last few years. A recent meta-analysis of publicly available gene-expression and clinical data totaling 2833 breast tumors provides 3 strong messages:

1. The published multigene signatures, despite the disparity in their gene lists, show similar prognostic information.
2. Proliferation is the biological process that has the strongest impact on clinical outcome, at least for the first few years following loco-regional therapy.
3. Tumor size and nodal status retain their prognostic information in a multivariate model.

However, strong claims about the clinical value of these signatures cannot be made without prospective clinical trials that validate their benefit above and beyond the use of standard clinico-pathological prognosis variables.

Two gene expression predictors, namely the 21-gene recurrence score (ONCOTYPE DX) and the 70-gene Amsterdam signature (MAMMAPRINT®) have reached the final step of prospective clinical trial testing.

In the MINDACT trial, 6,000 node-negative early breast cancer patients will have their risk assessed through standard clinical-pathological factors and through the new prognostic tool Mammaprint. To bring homogeneity and standardization to the risk assessment done in the control arm, this will be done through a modified version of the Adjuvant Online! program. Three scenarios are possible: (a) both methods classify the patient as high risk and, in this case, chemotherapy will be proposed; (b) both methods classify the patient as low risk and, in this case, chemotherapy will not be proposed; (c) the methods are discordant in their results and the patient will be randomized between "follow the genomic risk results" or the standard method. With this design it is estimated that 10 to 20% less patients will be spared adjuvant chemotherapy without any negative impact on their outcome, with obvious advantages for the patients and for health care systems.

In the TAILORx trial, 10,500 node-negative ER+ early breast cancer patients will be screened and have their risk assessed by the Oncotype Dx score. Patients with a score bellow 11, an estimated 29% of the population, will be proposed endocrine therapy only. Patients with a recurrence score higher than 25, an estimated 27% of the population, will be proposed chemotherapy in addition to endocrine therapy. The remaining 44% of the patient population (about 4,500), with a recurrence score between 11 and 25 will be randomized between endocrine therapy alone and chemo plus endocrine therapy. This is a non-inferiority design trial, where a decrease in 5-year DFS rate from 90% (with chemo) to 87% (without chemo) is defined as unacceptable.

The prediction is that these trials, TAILORx and MINDACT, will demonstrate a real improvement in the clinician's ability to evaluate prognosis, with a subsequent reduction in over- and under-treatment of women with adjuvant chemotherapy.

Aiming at the target: The development of adjuvant endocrine therapy has taught us 4 lessons: 1) the target plays a critical role; 2) it is important to measure the target accurately; 3) the duration of therapy matters; 4) progress depends on understanding modulators of the target.

Oncogenic redundancy, indeed, is recognized today as a significant obstacle to the success of targeted treatment and calls for "combinatorial and sequential therapies".

The development of high throughput platforms, which can provide parallel information on thousands of tumor genes and their correspondent proteins and the use of "synthetic lethality screens" in preclinical experiments should help with the identification of critical pathways and lead to smart combinations and/or sequences of targeted therapies.

A new dimension in the search for the right target: the stem cell: Gene-expression profiling studies have brought new information in the areas of breast cancer classification, prognosis and prediction of response to therapy.

Multigene prognostic "signatures", in particular, have taught us a critical lesson: not all the relevant information related to outcome is contained in the primary tumor gene expression profile. The Amsterdam and the Rotterdam prognostic signatures do carry strong prognostic information