Adjuvant Systemic Therapy, Quo Vadis? Patient Selection, Prognostic and Predictive Factors

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The evolution of scientific knowledge in these last few years has been quite astonishing in many areas, including oncology. Treatment individualization is no longer a dream but an achievable goal. Regarding adjuvant therapy, major advances have occurred in prognostication and patient selection, while progress has been slower for predictive factors.

New technologies such as gene expression profiling have helped us to prove breast cancer heterogeneity, a fact long seen in clinical practice. This is slowly leading to an important change in mentality of both researchers and clinicians regarding the optimal management of this disease. Considering breast cancer heterogeneity, we can no longer continue to treat all patients the same way, nor can we continue to run clinical trials in unselected breast cancer populations.

However, implementation of technologies that require the collection of frozen tumor samples, such as microarray or ELISA, in clinical practice, although possible demands adaptation of hospital logistics, true coordination within multidisciplinary teams, along with a new change of mentality. People tend to forget that, for decades, estrogen receptor determination required the collection of fresh frozen tumor samples and, due to the importance of this marker, hospitals and laboratories adapted. Improvement and quality control should be pursued in labs and hospitals all over the world. Additionally, and perhaps more difficult to overcome, these technologies and their implementation have high costs, which can be insurmountable for some parts of the world.

In addition to these logistic and economic hurdles, even with the use of new technologies, accurate patient selection continues to be very challenging and far from perfect. The new biological classification of breast cancer, based on gene expression profiles, into four main subgroups (HER-2, basal, luminal A and B) [1–4] only begins to dissect the complexity of breast cancer heterogeneity. The role of the pathologist is still crucial in establishing the diagnosis and determining histological type

and grade, since the role of molecular subtypes in histological types other than ductal carcinoma still needs further research. Additionally, there is a group of established biomarkers that are crucial for prognostication and prediction, particularly the estrogen receptor (ER), the progesterone receptor (PgR) and HER-2. These three markers are the only available predictive markers with level 1 evidence for the prediction of response to endocrine and anti-HER-2 therapies, respectively. For at least the next decade, patient selection will still need both ‘classical’ biomarkers and patients’ characteristics, as the ones used in the St. Gallen consensus guidelines [5] and the American Society of Clinical Oncology (ASCO) biomarker guidelines [6], as well as new biomarkers which are gaining widespread acceptance such as the urokinase-type plasminogen activator (uPa), the plasminogen activator inhibitor type 1 (PAI-1) (the only new biomarkers to achieve level 1 evidence) [7–9] and proliferation markers (such as Ki67) [10, 11]. In the meantime, biotechnologies such as gene expression profiling and proteomics will continue to evolve and be transformed into more ‘user-friendly’ tools that will enable their use in routine clinical practice. Two of these new tools will soon achieve enough level of validation to be accepted for routine use: the reverse transcriptase-polymerase chain reaction (RT-PCR)-based Oncotype DX™ (Genomic Health, Inc., Redwood City, CA, USA) [12] and the microarray-based MammaPrint™ (Agendia, Amsterdam, The Netherlands) [13, 14]. Two large prospective, randomized, adjuvant trials are ongoing to validate these tools – the MINDACT trial (EORTC 10041 BIG 3–04 trial; ClinicalTrials.gov identifier NCT00433589) [15, 16] for MammaPrint and the TAILORx trial (ClinicalTrials.gov identifier NCT00310180) for Oncotype DX.

Prediction of response to different types of systemic therapy has proved to be far more challenging, with no new markers or tools available despite innumerable research efforts in this area [17]. The reasons for this are also unclear. One could speculate

that, unlike the so-called targeted agents, chemotherapy acts through a non-specific mechanism of action and therefore only markers of response to chemotherapy in general such as proliferation markers can be identified and not markers of response to individual drugs. However, except for alkylating agents, all cytotoxic drugs do have specific targets, such as topoisomerase-II for anthracyclines and microtubules for taxanes. Despite this fact, the presence of the target by itself is not sufficient for predicting response. This fact is also seen with targeted agents such as anti-HER-2 therapies for which the presence of HER-2 is necessary but not sufficient to predict and obtain response. This is perhaps not surprising in view of the immense complexity of the cancer cell, where plasticity, adaptation and redundancy are key components that enable it to eventually overcome the effects of all available therapies. Only the continuing efforts in understanding this biological complexity, and particularly the key characteristics that differentiate a cancer cell from its normal counterpart, will open the necessary doors to the development of more effective treatments. The greatest challenge for research in oncology for the next decades will be to identify the ideal target, which should be a substance unique to cancer cells and absent from normal counterparts, accessible to external manipulation and crucial for the development or the progression of cancer. This challenge is deeply increased by the fact that we are fighting the self and not an external invader; tumor similarity to wounds [18] is much greater than to an infectious agent.

Another important area of active research is serial evaluation of disease biology, especially minimal residual disease. The largely discussed theory of a cancer stem cell needs to be further developed and substantiated. If indeed this theory is valid, then therapeutic efforts should focus on eradication of

these specific cancer cells in order for a cure to be achieved. The changes in cancer biology induced by treatment itself are another major area of research. This is particularly important in the advanced setting, but also after neoadjuvant treatment. Serial biopsies of both tumor sites and bone marrow have proven quite difficult to implement in current practice. Eventually, advances in nanotechnology and/or blood-based methods will help us overcome this difficulty.

Whatever the method chosen, collection and storage of as much biological material as possible and according to common and well-established guidelines [19] is indispensable. In fact, it can even be considered the rate-limiting hub for all cancer research. Cell lines and animal models have been good tools, but their pitfalls and limited translation to humans are also well documented. Only research based on human samples and/or human subjects has the true potential to lead the way for breakthroughs in the fight against cancer. The technological advances in the last decades have been so rapid and deep that researchers of today must be foresighted and creative in collecting the material that will be needed for tomorrow's research. Only time can give us the most needed long follow-up, but it is our responsibility to collect the available material, foremost for the benefit of the patient.

Knowledge is an accumulation of experiences, which both success and failures contribute to, and where 'new' does not replace the old but adds to it. Decades of research efforts of dedicated scientists, clinicians and patients have taught us invaluable lessons about cancer biology and treatment. Individualized treatment is at the doorstep, not necessarily with 'targeted' agents, but certainly with tailored therapies that are adjusted not only to the cancer cell specificities but also to the individual patient's characteristics.

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