EDITORIAL

Genome-based diagnostics and therapeutics in personalized cancer therapy: Can the challenges be overcome?

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Abstract

With isolated success – trastuzumab, imatinib, vemurafenib-, the current generation of targeted drugs provides limited benefit for cancer patients. Evidence from phase 3 randomized trials suggests mostly progression-free survival benefit without a true overall survival prolongation. The advent of high-throughput technologies and advances in systems computational biology shape now high expectations for the next-generation cancer-targeted drugs and biomarkers. This new era of personalized medicine raises hope for individual tumor-heterogeneity-based implementation of targeted drugs. Which are the challenges and how could be possible to overcome therapeutic resistance of cancer cells and to increase cancer therapy efficacy and improve oncological outcomes?

Targeted therapy assessment

As a general conclusion about cancer targeted drugs is that their efficacy is temporary for a few a few months followed by disease progression. Low or no antitumor activity for most currently available targeted cancer drugs has been revealed by recent phase 3 randomized trials. Although trastuzumab and imatinib show long-term therapeutic effects in gene defects-based selection of patients curing many of them, they are also limited by acquired resistance in other patients while vemurafenib response and overall survival benefit is fleeting with acquired resistance after a mean duration of ~7 months. Besides this clinical success, for all others monoclonal antibodies (mAb) and small-molecules tyrosine kinase inhibitors (TKI) evidence suggests either a progression-free survival without an overall survival benefit or no therapeutic effect1. How can be explained these clinical results despite highly promising data from research arena? The revolutionary next-generations sequencing (NGS) technologies provide an unprecedented capacity for whole-genome sequencing (WGS), whole-exome sequencing (WES), and RNA sequencing (RNA-seq)-based transcriptome analysis. Can these genome-wide mapping technologies applied in appropriately designed clinical trials lead to overcoming resistance to current drugs and poor clinical outcomes by improving therapeutic approaches with personalized oncology implementation into clinic?
Translational oncology

Over the past decades, evidence-based standardization of surgery, radiotherapy and systemic chemotherapy has resulted in substantial survival benefit of million of cancer patients. However, despite multiple enthusiastic reports, the hard reality is reflected by the current US cancer statistics with cancer death rates to remain alarmingly high particularly in advanced tumor stages III and IV. In addition, adverse effects of systemic chemotherapy have slowly been reduced influencing quality of life.

To increase the efficacy regarding responsiveness and survival rates, pharmaceutical and biomolecular diagnostic industry has been shifted from chemotherapy to signalling transduction-inhibitor drugs development and validation. Crucial cellular process including survival, grow, differentiation, proliferation and apoptosis are regulated by signalling transduction from cell surface to the nucleus. Deregulation or amplification of this signal transmission by the accumulation of genetic and epigenetic changes and ultimately also gene expression dysfunction, collectively result in major diseases such as cancer, among others.

Inhibiting or restoring deregulated signaling pathways and gene expression patterns in cancer cells is the main principle in the effort to develop effective signal transduction drugs. This targeted therapy provides theoretically a dual effect. By targeting only cancer cells, the signal transduction drugs can potentially kill cancer cells without affecting healthy normal cells and thus reducing side effects. The US Food & Drug Administration has presently approved 33 mAb and TKI for metastatic cancer, one only for clinical treatment of solid tumors in the adjuvant setting while a large number of signalling pathways inhibitors is in clinical development.

Personalizing therapy

Clinical evidence has established the concept of personalized treatment by selecting cancer patients not only on the basis of clinicopathologic characteristics and tumour-node-metastasis (TNM) staging but also of gene defects and signalling pathway deregulation underlying cancer cells. Although trastuzumab and vemurafenib represent two targeted cancer drugs with clinical success, they represent the exception in the general rule of fleeting or no anticancer effect of targeted drugs. Unlike most tumor-guided drugs, solid evidence suggests that the anti-human epidermal growth factor receptor 2 (HER2) humanized mAb trastuzumab improves overall survival in HER2-positive metastatic breast and gastric cancer and it is the unique targeted drug approved in the adjuvant setting among all solid tumors specifically for the treatment of early stage breast cancer. The TKI vemurafenib (PLX4032) for patients with metastatic melanoma and BRAF V600E mutation has provide evidence that significantly improves overall survival. Resistance remains a challenge even among selected patients on the basis of HER2 amplification and protein overexpression or BRAF mutation respectively. This intrinsic (primary) or acquired (secondary) resistance and recurrence or disease progression results in a long-term permanent anticancer effect in a proportion only of treated patients. How can be overcome trastuzumab resistance? Adding lapatinib to trastuzumab in the neoadjuvant chemotherapy of HER2-positive breast cancer patients, pathological complete response (pCR) could significantly be improved in the NeoALTTO phase 3 Study. This higher response rate may reflect a significant reduction in resistance and recurrence rate but it requires a long-term overall survival benefit confirmation in phase 3 randomized trials. By contrast, neither the addition of pertuzumab, another anti-HER2 mAb, to trastuzumab and chemotherapy in metastatic HER2-positive breast cancer patients nor the addition of the mammalian target of rapamycin (mTOR) inhibitor everolimus to endocrine therapy in hormone-receptor-positive patients improved overall survival. In metastatic melanoma, Vemurafenib improved overall survival but this benefit was transitory with disease progression to occur after a mean duration of 7 months suggesting the appearance of acquired resistance and disappear of survival curves difference between vemurafenib and control group after 7 months.
Unlike trastuzumab and vemurafenib, for the vast majority of other targeted drugs, the results from phase 3 randomized trials in the treatment of solid tumors are less promising. Either a progression-free survival only improvement without any overall survival benefit or no treatment response has been reported\(^1\)\(^3\)\(^4\). Most of currently approximately 150 kinase-targeted drugs are in clinical development and many more in various stages of preclinical development are in oncology indications but evidence from current phase 3 trials limits the expectations in temporary or no antitumor effect and no overall survival benefit\(^1\)\(^4\).

**Changing the research arena**

Two major research directions are now being shaped to overcome targeted drugs resistance and poor clinical outcomes. Either intrinsic (primary) or acquired (secondary) resistance, the result is treatment failure and patient’s death. First, in translational medicine improved patient’s stratification for optimizing tailored therapy from available targeted drugs can be resulted from mutational landscape revealed by sequencing patient’s tumour through NGS\(^1\)\(^4\)\(^5\). Second, in innovative research, next-generation drugs can emerge by using NGS, network biology and systems science approach to explore, understand and predict cellular signalling transduction interactions network\(^5\)\(^6\)\(^7\). Ultimately, to change traditional concept “one-size-fits-all” and move to “multi-scale molecular interactions network” for achieving a pragmatic precision medicine, evidence from phase 3 trials will be essential before wide clinical application\(^8\)\(^9\)\(^10\).

The advent of NGS technologies has so dramatically changed biomedical research within the last six years, that we discuss whether it is now the time to translate these genome-wide mapping technologies into clinical use. For example, it is evaluated the potential of introduction of NGS platforms in large pathology laboratories for sequencing patient’s tumour samples\(^10\)\(^21\). The free falling costs of a human’s genome sequencing and the validity of sequencing data not only raise the questions for clinical implementations but also allow a democratization of research moving from “big” to “low” costs of scientific programs\(^22\)\(^23\).

**Exciting findings are currently reported** by applying high-throughput technologies in both primary tumours and metastatic biopsies allowing for a comprehensive genome, epigenome and transcriptome analysis. These new studies provide potential implementations in a novel mutations-based taxonomy\(^1\)\(^4\), personalized cancer diagnostics\(^24\)\(^26\), and optimizing decision for personalized cancer targeted therapy\(^27\).

Ding et al\(^24\) provide now complementary information on clonal evolution to recently described mutation clonal analysis for breast and pancreatic cancer metastases. Determining the mutational spectrum at the primary tumour and relapsed genomes from eight patients with AML, they found two major clonal evolution patterns during AML relapse. In the first, the founding clone in the primary tumor gained new mutations and evolved into the relapse clone. In the second, a subclone of the founding clone survived initial therapy, gained additional mutations and expanded at relapse\(^24\). Taken together, these clonal evolution data on breast and pancreatic metastatic cancer\(^28\)\(^31\) and AML\(^24\) suggest that some mutations and DNA-damage chemotherapy may contribute to clonal selection and initial therapeutic resistance. Given the wide inter-patient and intra-tumour heterogeneity, tumour sequencing providing a whole picture of cancer-initiating and metastatic-causing mutations in individual patients can lead to personalized cancer medicine.

Chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq) provides a fascinating technology for transcriptome mapping at a genome-wide level. As oestrogen receptor (ER) is the defining transcription factor and its target genes orchestrate growth and endocrine response, ER-binding events could be used to assess therapeutic response and prognosis. Shifting from cell-lines models to clinical samples, Ross-Innes et al\(^25\) for the first time mapped genome-wide ER-binding events by ChIP-seq, in frozen primary breast cancers samples from
patients with good and poor clinical outcomes and in distant ER-positive metastases. They found that unique ER-binding regions in primary tumors were associated with relapse and poor outcome. Unlike with the report by Ding et al in AML 24 and another breast cancer report on clonal evolution 28, Ross-Innes et al 25 found that the differential ER-binding programme observed in tumours from patients with poor outcome was not due to the selection of a rare subpopulation of cells, but was due to the FOXA1-mediated reprogramming of ER binding on a rapid timescale. This ChIP-seq-based transcription-factor mapping in primary tumour material provides therefore the potential for discovering novel biomarkers to predict therapeutic response and outcome in individual patients.

In the third study, Roychowdhury et al 27 extracted DNA and RNA both from samples of two patients with metastatic solid cancer and applied the “sequence everything” approach for NGS-based WGS, WES and (RNA-seq) for transcriptome mapping as well as gene expression. This sequencing strategy allowed in the assessment of all classes of genetic variants including, point mutations, copy number alterations and genomic rearrangements, as well as gene amplification and overexpression. Subsequently, a multidisciplinary Sequencing Tumor Board analyzing and interpreting the results identified several genetic alterations in each patient. Among all these genetic changes, the Board considered important for clinical trials, the identified amplification of cyclin-dependent kinase 8 (CDK8) and thus CDK inhibitors or MEK (mitogen-activated or extracellular signal-regulated protein kinase) in the first patient with colorectal cancer has been proposed. The identified Ras mutation in the second patient with melanoma provides the rationale for PI3K (phosphatidylinositol 3-kinase) inhibitors. Roychowdhury et al suggest that this comprehensive mutational landscape of individual patient’s samples by integrative high-throughput sequencing facilitates clinical trials for drugs targeting patient’s activating signalling pathways and precision oncology 27.

Conclusions
Overcoming the problems
The emerging NGS-based biomedical and clinical research shapes now two major fascinating goals. First, to optimize therapeutic approaches by tailoring combinations of available chemotherapeutics and targeted drugs in responder WGS/WES and transcriptome mapping-based individual selected patients. Second, in a more distant future to develop novel drugs based on a combination of an individual patient’s cancer genome with respect to both his/her structural mutations landscape and deregulation of functional signalling transduction interactions network and biological circuits.

References


