Current Challenges in Cancer Treatment

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ABSTRACT

Purpose: In this review, we highlight the current concepts and discuss some of the current challenges and future prospects in cancer therapy. We frequently use the example of lung cancer.

Methods: We conducted a nonsystematic PubMed search, selecting the most comprehensive and relevant research articles, clinical trials, translational papers, and review articles on precision oncology and immuno-oncology. Papers were prioritized and selected based on their originality and potential clinical applicability.

Findings: Two major revolutions have changed cancer treatment paradigms in the past few years: targeting actionable alterations in oncogene-driven cancers and immuno-oncology. Important challenges are still ongoing in both fields of cancer therapy. On the one hand, druggable genomic alterations are diverse and represent only small subsets of patients in certain tumor types, which limits testing their clinical impact in biomarker-driven clinical trials. Next-generation sequencing technologies are increasingly being implemented for molecular prescreening in clinical research, but issues regarding clinical interpretation of large genomic data make their wide clinical use difficult. Further, dealing with tumor heterogeneity and acquired resistance is probably the main limitation for the success of precision oncology. On the other hand, long-term survival benefits with immune checkpoint inhibitors (anti–programmed death cell protein-1/programmed death cell ligand-1 [PD-1/L1] and anti–cytotoxic T lymphocyte antigen-4 monoclonal antibodies) are restricted to a minority of patients, and no predictive markers are yet robustly validated that could help us recognize these subsets and optimize treatment delivery and selection. To achieve long-term survival benefits, drug combinations targeting several molecular alterations or cancer hallmarks might be needed. This will probably be one of the most challenging but promising precision cancer treatment strategies in the future.

Implications: Targeting single molecular abnormalities or cancer pathways has achieved good clinical responses that have modestly affected survival in some cancers. However, this approach to cancer treatment is still reductionist, and many challenges need to be met to improve treatment outcomes with our patients. (*Clin Ther.* 2016;▮:▮▮▮–▮▮▮)

Key words: cancer therapy, checkpoint inhibitors, drug development, immunotherapy, lung cancer, next-generation sequencing, precision oncology, targeted therapy.

INTRODUCTION

Cancer is a major public health problem worldwide. Global demographic characteristics predict an increasing cancer incidence in the next decades, with >20 million new cancer cases annually expected by 2025. According to GLOBOCAN data, 14.1 million new cases and 8.2 million deaths from cancer were estimated in 2012.[1] Cancers of the female breast, colorectal, prostate, and lung are the most frequently diagnosed cancers in Europe.[2] Lung cancer remains the leading cause of cancer incidence and mortality worldwide.[1]

The increasing knowledge of molecular and tumor biology has notably changed cancer treatment paradigms during the past 15 years. Formerly, cancer was classified and treated solely according to organs of origin or simplistic histomorphologic features. In a seminal paper published by Schiller et al[3] in 2002,

The basis for this article has been presented as a Keynote Lecture at the 12th Congress of the European Association of Clinical Pharmacology and Therapeutics in Madrid, Spain.

Accepted for publication March 17, 2016.

http://dx.doi.org/10.1016/j.clinthera.2016.03.026

0149-2918/$ - see front matter

completely overlapping survival curves were found in advanced non–small-cell lung cancer (NSCLC) patients after use of 4 different platinum-based chemotherapy doublets with third-generation drugs. Even though the trial was limited to lung cancer, it found that cancer treatment based on a broad use of cytotoxic chemotherapies in unselected patients had reached its therapeutic plateau. In addition, it became clear that the development of molecularly targeted therapies and treatment selection based on particular molecular alterations was needed. Since then, 2 pillars have driven the subsequent evolution of cancer treatment: new technology acquisition for tumor molecular profiling and the discovery of predictive molecular targets. Together, these efforts have materialized the 2 recent revolutions in cancer treatment. First, genotype-directed precision oncology, that is, tailoring personalized therapies to subsets harboring specific genomic abnormalities across different tumor types. Second, targeting components of the tumor microenvironment, in particular the immune system and the antitumor immunity. In this review, we will succinctly describe the fundamental premises of these 2 anticancer strategies. We will also highlight some of the major challenges ahead in both fields of cancer treatment, frequently using the example of lung cancer.

METHODS

We did a nonsystematic review of current concepts in precision oncology. References for this review were identified through searches of PubMed using the terms *precision oncology* (8301 results; 313 clinical trials), *oncogene addiction* OR *targeted therapies* (102,601 results; 4883 clinical trials), *next-generation sequencing* OR *early drug development* (69,901 results; 2201 clinical trials), *immunotherapy* OR *immuno-oncology* (255,507 results; 14,081 clinical trials), *immune checkpoint inhibitors* OR *PD-1/L1 blockade* (769 results; 17 clinical trials), and *non–small-cell lung cancer*. Articles were selected mainly on the basis of their clinical applicability, and we prioritized for practice-changing clinical studies, some translational papers, and selected comprehensive reviews published in the last 5 years. Relevant articles were also identified through searches of the authors' files and when reviewing other papers and their respective bibliographies. Unpublished reports from scientific conferences were identified across meeting libraries and abstract books. Only articles published in English were included. All of the references cited in this article were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

TARGETING ACTIONABLE ALTERATIONS IN ONCOGENE-DRIVEN CANCERS

The essential premise of genotype-based precision oncology is that tumor-specific molecular abnormalities can be targeted with accurate, effective, and potentially less-toxic therapies. Extensive preclinical work and primary discoveries of somatic, single-gene genomic abnormalities that could be pharmacologically targeted opened the first gateways for genomic precision oncology. More recently, comprehensive and integrative characterization of many cancers using high-throughput technologies under the auspices of national (eg, The Cancer Genome Atlas, funded by the National Cancer Institute and National Human Genome Research Institute in the United States) or international (eg, International Cancer Genome Consortium) efforts, has led both to a new era of genomic or molecular taxonomy of cancer and to the discovery of cancer genes and biomarkers for therapy.[4]

There are 3 crucial issues for successful clinical biomarker development: biologic plausibility (the identified genomic alteration is responsible for malignant transformation and tumor progression), analytical validity (it can be detected with robust, reliable, and clinically applicable genomic tests), and clinical validity (the prognostic or predictive utility of the biomarker has been validated in clinical trials and community-based clinical cohorts). At the same time, it must be emphasized that clinical biomarkers might have diagnostic, prognostic, predictive, or pharmacogenomic utilities.[5] Predictive biomarkers are the most useful markers in daily practice, as they simultaneously enable both selection of subsets that will obtain the greatest benefits from a certain treatment and exclusion of those who will not benefit from therapy. Prognostic markers, however, are informative of patient outcomes irrespective of treatment, and are therefore less frequently used in the clinic for treatment decisions.

NSCLC is one example that illustrates the paradigms of genomics precision oncology. From the initial one size fits all described in the study by Schiller