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Opinion

Cancer Disease-Oriented-Drug Development Examples

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ABSTRACT

The history of cancer medical treatments goes up to 1908 with the use of arsenic in this disease. An intermediate milestone was the discovery, in 1943, of an amazing tumor response using nitrogen mustard in a patient with a radio-resistant lymphoma. Chemotherapy really born with this achievement, and a plethora of antitumor agent's came to age after 1948 till nowadays. Here, some examples of recent disease-oriented drug development approaches are presented and analyzed, as well as present limitations and challenges raised by each one.

Keywords
Cancer; Neoplasms; Chemotherapy; Antitumor agents; Drug development.

INTRODUCTION

The approval of Imatinib in 2001 for the chronic myeloid leukemia (CML) highlighted a new therapeutic concept due to its novel mechanism of action and the exceptional tumor response and survival outcome observed in relapsed patients, otherwise condemned to death after resistance to previous chemotherapy schemes. The before-mentioned made of this drug the first real masterpiece of the new millennium.[1] In parallel with new technological developments and new drug discovery/delivery to the clinical setting, the apparition of genomics and proteomics is considered to be a seminal advance in oncology, increasing our understanding of cancer biology since the nineties. From then up-to-now, we have increased basic research and clinical opportunities with more targets and molecules than ever, molecules with desirable features as higher specificity, higher selectivity and lower toxicity. There are also new drug development issues that apply special strategies just from their inception: increased therapeutic index, more effectiveness in the resistant disease, replacement of previous drugs not always necessary, as well as disease-oriented drugs. This last type of drugs, with novel activities and/or sites of action, are developed according to pharmacological issues but also to the biology of a specific tumor model. Then the use of this strategy is exemplified in five tumor models: non-small cell lung carcinoma, breast carcinoma, ovarian carcinoma, melanoma and lymphoma.

Some Examples

Non-small cell lung cancer (NSCLC), the most prevalent carcinoma in many parts of the world, is a deadly disease with some interesting features to mention. First, it has many oncogene drivers, being Kirsten rat sarcoma viral oncogene homolog (KRAS) or Ki-ras2 the prevailing one (with the recent outstanding outcome of the G12C pocket-inhibitors, such as Sotorasib with its rational treatment of this now druggable oncogene).[2] Second, it presents signaling pathways with the potential to be tackled by specific inhibitors (epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors for e.g.), that in some cases have also activity in brain Mets control. Indeed, their antitumor effect in second- and third-line treatments is at present a reality. Nevertheless, the main issue now is to unveil main drug-resistance mechanisms of this type of tumor in order to overcome them.[3]

When developing a new drug, some important factors must be considered, as: pharmacokinetics, pharmacodynamics, specific drug-resistance mechanisms and chemosensitivity, among others. Breast cancer, the prevalent tumor in women, is to be considered as "many different diseases". Specifically, pre/post-menopause, triple-negative breast carcinoma (TNBC) presents acquired resistance and high tumor heterogeneity. New disease-related drug development must in this case consider agents active in second- and third- lines of treatment without cross-resistance.

New biology interventions came to breast cancer treatment several years ago, with the discovery of human epidermal growth factor receptor (HER2) inhibitors (Herceptin), bone remodeling agents (zoledronic acid), hormones with different mechanisms of action at the estrogen receptor, new cytostatics that quite changed the natural disease history in a metastatic setting, cell-cycle inhibitors and poly-ADP ribose polymerase (PARP) inhibitors, among others. Recently, the introduction of therapeutic vectorized antibodies (monoclonal antibodies (mAbs)) such as immunotherapy with checkpoint inhibitors, is trying to gain territory to overcome this malignancy, as is the case with Pembrolizumab in TNBC.[4]

Treatment of ovarian carcinoma is another interesting example of what it means a disease-oriented therapeutic approach.[5] This disease has a special natural history of "peritoneal disease", which adds complexity to the pharmacokinetics and pharmacodynamics of the delivered drugs. As a matter of fact, when trying to improve clinical results, the intraperitoneal delivery of cytostatics has been evaluated in many trials, some of them randomized, even though they are not yet accepted as standard of care, and not all centers are able to work with them. A second-line treatment is a "must", but there is no disease- modifying agents at this stage, except for some novel ones in Clinical Trials ending and waiting for future approvals. In the meantime, we use antiangiogenics combined with chemotherapy but this does not surpass the problem of drug resistance. Many old drugs still work in third- or fourth-line treatments such as oral alkylating agents (mainly Melphalan), giving the patients clinical benefits and maintaining quality-of-life (QoL) issues. Novel drugs such as PARP inhibitors (Olaparib) have proved their worth in maintaining the disease-free status and prolonging survival in the advanced disease after initial chemotherapy.

Melanoma, a tumor model with "elusive" immunogenicity, remains totally chemo-resistant after nearly five decades of an absence of disease-modifier compounds. Fortunately, the apparition of biological response modifiers as interferon alfa and cytokines such as interleukin-2 (IL-2) presented us a better and promising treatment landscape. In fact, since 2011 we are living in a new therapeutic era: the immuno-oncology era. The use of checkpoint inhibitors present awesome results in many tumors, as aforementioned, but mainly in melanoma. With these immune compounds, previous natural therapeutic history of melanoma has been completely changed. We now often assist to tumor complete responses, with control of brain Mets and prolonged no evidence of disease (NED) patient status, leading in some cases to the complete cure. The still-to-solve problem here is to better understand the mechanisms of resistance at relapse.

The last example here presented is related to lymphomas that, even considered as" many diseases", are always very chemosensitive tumors with fast cell kinetics that leads to cure in many cases. Therapeutic vectorized antibodies (Rituximab) today represent the standard of care in combination with classical chemo (CHOPP). Novel interesting drugs such as Ibrutinib are able to beat new targets such as the Bruton's tyrosine kinase (BTK) pathway and are already in the clinical arena with outstanding clinical results.[6] These new agents must surely be active soon in third-line treatments.

In this breviary, only a few tumor models have been chosen in order to describe the disease-oriented drug development strategy and to assess some of the clue issues that impede the achievement of better clinical results. Cancer is an extremely complex disease, and its different types may be studied from several sides and points of view. Disease-oriented therapeutic approaches can be an interesting and promising way to cope with its complexity and accomplish the cure.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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