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Review

Targeted cancer therapy – Are the days of systemic chemotherapy numbered?

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ABSTRACT

Targeted therapy or molecular targeted therapy has been defined as a type of treatment that blocks the growth of cancer cells by interfering with specific cell molecules required for carcinogenesis and tumor growth, rather than by simply interfering with all rapidly dividing cells as with traditional chemotherapy. There is a growing number of FDA approved monoclonal antibodies and small molecules targeting specific types of cancer suggestive of the growing relevance of this therapeutic approach. Targeted cancer therapies, also referred to as "Personalized Medicine", are being studied for use alone, in combination with other targeted therapies, and in combination with chemotherapy. The objective of personalized medicine is the identification of patients that would benefit from a specific treatment based on the expression of molecular markers. Examples of this approach include bevacizumab and olaparib, which have been designated as promising targeted therapies for ovarian cancer. Combinations of trastuzumab with pertuzumab, or T-DM1 and mTOR inhibitors added to an aromatase inhibitor are new therapeutic strategies for breast cancer. Although this approach has been seen as a major step in the expansion of personalized medicine, it has substantial limitations including its high cost and the presence of serious adverse effects. The Cancer Genome Atlas is a useful resource to identify novel and more effective targets, which may help to overcome the present limitations. In this review we will discuss the clinical outcome of some of these new therapies with a focus on ovarian and breast cancer. We will also discuss novel concepts in targeted therapy, the target of cancer stem cells.

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1. History of targeted cancer therapy

Targeted cancer therapy has attracted public attention with the hope that it will be possible to replace systemic chemotherapy in the future. This 'magic bullet' therapy is expected to be more effective and less harmful than systemic chemotherapy because the aim of targeted cancer therapy is to block specific pathways related to carcinogenesis and tumor growth by inducing apoptosis of cancer cells, blocking specific enzymes and growth factor receptors involved in cancer cell proliferation, or modifying the function of proteins that regulate gene expression and other cellular functions, rather than by simply interfering with all rapidly growing cells. If it is possible, the goal of cancer treatment in the future will be shifted from 'cure' to 'management' and cancer patients will not be expected to experience hair loss, which is still a stereotype of systemic chemotherapy.

Surprisingly, this concept is nothing new and it has been available for a long time. A classical model of targeted cancer therapy is ^{131}I therapy for thyroid cancer. Thyroid cancer cells exclusively uptake iodine by its iodine receptor and the accumulated radioactivity of ^{131}I kills thyroid cancer cells [1]. This targeted therapy for thyroid cancer has been used successfully since the 1940s [2]. A more typical model of molecular targeted therapy is tamoxifen, a selective estrogen receptor modulator (SERM). It binds to estrogen receptors competitively and antagonizes them in breast tissue. Because some breast cancer cells require estrogen to grow, tamoxifen has been used to prevent recurrence of estrogen receptor-positive breast cancer for pre- and post-menopausal women [3].

One of the first breakthrough of molecular target biology was imatinib, used for the treatment of chronic myeloid leukemia (CML). Philadelphia chromosome, a unique characteristic of CML, is related to BCR-Abl tyrosine kinase overexpression, which does not occur in normal cells. Therefore, this selective BCR-Abl tyrosine kinase inhibitor, imatinib, could suppress the growth of Philadelphia chromosome-positive CML with less harm to normal cells [4]. Thereafter, CML seemed to become a 'manageable' disease, like hypertension or diabetes. Imatinib was also found to be effective in gastrointestinal stromal tumor (GIST) with c-kit overexpression [5].

Due to the success of targeted cancer therapy in CML, a number of new drugs were developed for the treatment of solid tumors. Unfortunately, not all these new drugs were found to be effective in the majority of the tested tumor types. Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, is an example of a new therapy that the U.S. Food and Drug Administration (FDA) initially approved for the treatment of non-small cell lung cancer (NSCLC). Two years later, the FDA withdrew the approval of gefitinib due to lack of evidence that it improved survival of patients [6]. The FDA also removed bevacizumab, a monoclonal antibody that inhibits angiogenesis, because of its lack of efficacy in breast cancer patients and its numerous side effects [7]. In spite of these early disappointments, new-targeted cancer therapies are still under active investigation.

2. Categories of targeted therapies

Two categories of targeted cancer therapy include small molecules and monoclonal antibodies. Small molecules are referred to low molecular (less than 800 Da) organic compounds. These 'small molecules' can penetrate the cell membrane and are designed to interfere with signaling pathways and to act on targets found inside the cell. Most monoclonal antibodies cannot penetrate the cell's plasma membrane and are designed against targets outside the cell or on the cell surface. The name of a targeted therapy provides a clue to the type of agent and its cellular target. Small molecules that have "-ib" as a suffix indicate a molecule that has inhibitory properties. Many of these molecules are developed as tyrosine kinase inhibitors. Imatinib and gefitinib, mentioned above, are typical examples of small molecules with inhibitory potential. Erlotinib is an EGFR tyrosine kinase inhibitor and works similarly to gefitinib. Recently it was shown in the SATURN (Sequential Tarceva in Unresectable NSCLC) study that erlotinib was significantly better than gefitinib as maintenance treatment for advanced non-small cell lung cancer (NSCLC) [8]. Therefore erlotinib has replaced gefitinib for advanced NSCLC.

"Monoclonal antibodies" are designated humanized antibodies, which bind to cancer cell-specific antigens. Monoclonal antibodies have "-mab" as a suffix. The FDA approved four kinds of monoclonal antibodies for the treatment of solid tumors: bevacizumab, cetuximab, panitumumab, and trastuzumab. Bevacizumab targets vascular endothelial growth factor (VEGF). It is approved for colorectal cancer, NSCLC, metastatic renal cancer and glioblastoma multiforme. Trastuzumab targets HER2/neu receptor and is used for HER2-positive metastatic breast cancer. Cetuximab and panitumumab target EGFR and are approved for metastatic colorectal cancer. Another therapeutic application for these monoclonal antibodies is their use as drug delivery system or antibody-drug conjugate (ADCs). When a monoclonal antibody binds to cancer cells, the cytotoxic drug conjugated with the antibody is engulfed into the cancer cells, and released intracellular inducing specific cell death. This technology provides a wider therapeutic range by targeting cancer cells and by reducing the potential side effects of the cytotoxic compound. The pioneer of ADCs was gemtuzumab-ozogamicin, approved for acute myeloid leukemia (AML) in 2001. But it was withdrawn from the market at the request of the FDA in 2010 [9,10]. In 2011, the FDA approved brentuximab-vedotin for relapsed and refractory Hodgkin lymphoma and anaplastic large cell lymphoma [11]. In 2013, Ado-trastuzumab emtansine (T-DM1), which is trastuzumab linked to DM1, was approved by the FDA for HER2-positive metastatic breast cancer [12].

3. Personalized medicine and The Cancer Genome Atlas (TCGA)

The successes and failures of these small molecules and antibodies further demonstrate the complexity of the tumor biology and the need to identify new specific pathways. Clearly, it will be very difficult to have a single therapy for all cancers, not even for a single type of cancer. Therefore, the concept of personalized medicine becomes relevant and points to the need to evaluate every patient according to his/her unique tumor phenotype. Consequently, the next step of targeted cancer therapy is the identification of new specific targets. The identified target molecules will then be used for the identification of the specific sub-population of patients who have the receptor of the identified target molecule and therefore could benefit from the treatment. This is the major aim of "Personalized medicine". Future FDA approval of a targeted therapy will be based on the identification of new drugs for a specific population of patients who have a specific marker. An example of this approach is trastuzumab, a monoclonal antibody that interferes with the HER2/neu receptor. An HER2 assay is required to administer trastuzumab because only patients that test positive for HER2-metastatic breast cancer have FDA approval to receive the drug.

Next generation sequencing (NGS) made whole-genome sequencing of cancer samples become a reality and enabled comprehensive research of cancers' genome [13]. One of the biggest studies using this approach was The Cancer Genome Atlas (TCGA) project, whose aim was to reveal molecular aberrations that are