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Review Article

Targeted Chemotherapy- A Review

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Abstract

Targeted therapies are the drugs which are designed in order to interfere with the specific molecules necessary for the tumor growth and progression. The traditional cytotoxic chemotherapies mostly kill the rapidly dividing cells in the body by interfering with the cell division while causing the toxicity in normal cells also. This review article aims to highlight the most recent FDA-approved anticancer drugs eligible for targeted therapies. In addition, an early outline evaluation of the costs of the therapies was also taken in consideration. Moreover, further studies have been going on in order to plan treatment regimen for these drugs. On the basis of these fields, the oncologists will have new means to make treatment decisions for their patients in order to maximize benefit and minimize toxicity.

Keywords: Monoclonal antibodies, Small molecules, Targeted therapies, Tyrosine kinase inhibitors.

INTRODUCTION

The prime objective of the targeted therapy is to inhibit the cancer cells with more precision and potentially fewer side effects. This is a promising reason therapy for the 3rd millennium and traditional cytotoxic chemotherapy works primarily inhibits the cell division. Apart from the fast growing cancer cells, the other rapidly dividing cells like hair, bone marrow and gastrointestinal epithelium etc are also affected by these drugs [1]. In contrast to the traditional chemotherapy, the targeted therapy only blocks the rapid proliferation of the cancer cells by interfering with the specific molecules required for the tumor growth and development. The prime drugs for targeted therapies are monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs) which interfere with the proteins and RNA molecules. These molecules are often overexpressed or mutated in tumors. The emergence of the targeted therapies, which include Small molecule inhibitors (SMinhs) and mAbs have significantly changed the treatment planning of cancer over the past 15 years. Targeted therapy is now a part of treatment for many common cancers like breast, lung, colorectal and pancreatic, leukemia, lymphoma and multiple myeloma [1, 2]. The mechanisms of action of these drugs and their toxicities differ from those of traditional cytotoxic chemotherapy. The targeted therapies are mostly better tolerated than the traditional chemotherapy, but they are associated with the several toxicities, like cardiac dysfunction, hypertension, acneiform rash, thrombosis and proteinuria, or the resistance because of the acquired mutations on target molecules. The small molecule inhibitors are metabolized by cytochrome P450 enzymes and are thereby subject to multiple drug interactions. The therapeutic monoclonal antibodies are the immunoglobulin structures which are designed to target the specific antigens found on the cell surface like extracellular growth factors or transmembrane receptors [3]. The monoclonal antibodies are in some cased conjugated to the toxin or radio-isotopes in order to allow the specific delivery of these cytotoxic agents to the intended cancer cell target. The small molecules are designed for interfering with the enzymatic activity of the target protein. These molecules can penetrate the cell membrane in order to interact with the targets inside a cancer cell. Like any other drug, the targeted cancer therapies typically have many different names. One or more names are used to identify the chemical compound during development; if successful, and then

the drug receives a generic name followed by a brand name which is used by the pharmaceutical company for marketing, for example, the small molecule STI-571 which is known as imatinib (generic name) and it is marketed by the Novartis under the brand name Gleevec™. The name of a targeted agent provides clues to the type of agent and its cellular target. The monoclonal antibodies end with the stem "-mab" (monoclonal antibody). They have an additional subsystem designating the source of the compound e.g., "-ximab" for chimeric human-mouse antibodies, "-zumab" for humanized mouse antibodies, and "-mumab" for fully human antibodies. The small molecules end with the stem "-ib" which indicates that the drug has protein inhibitory properties. Both small molecules and monoclonal antibodies contain an additional stem in the middle of the name describing the molecule's target; examples for monoclonal antibodies include "-ci- " for a circulatory system target and "-tu-" for a tumor target, while examples for small molecules include "-tin-" for tyrosine kinase inhibitors and "-zom-" for proteasome inhibitors. The earliest targeted therapies were antibodies directed against the cell surface markers cluster of differentiation 33 CD33, CD20 and CD52 which are present on the leukemia and cells [1-4]. Since CD20 is also present on the normal lymphoid cells, when this molecule is targeted; the overall immune function is affected. Thereby, this observation has led to the use of the anti-CD20 monoclonal antibody like rituximab for the treatment of autoimmune diseases such as rheumatoid arthritis and non- Hodgkin's lymphoma. The fragment antigen binding (Fab) of a monoclonal antibody, which is responsible for the recognition and binding with the antigens and it is responsible for the possibility of such therapies by specific targeting highly specific molecules. The mAbs exert their antineoplastic effects by various mechanisms such as by engaging the host immune functions to attack the target cell; by binding either to receptors or ligands, thereby blocking the crucial cancer cell processes. The other mechanism includes a lethal payload carrier like a toxin or radioisotope, to the target cell (i.e., conjugated mAbs) [3, 4]. As the protein structure mAbs is digested by the gastrointestinal fluids, they are administered intravenously. Moreover, because they donot undergo hepatic metabolism therefore they are not subject to significant drug interactions. In the past twenty years, the design of mAbs has changed as biotechnology has improved. Earlier the drugs for targeted chemotherapy were produced by immunizing the mice with target antigen. Thereby, the resulting mAbs were composed entirely of the mouse proteins, which have a potential risk for being very antigenic to the humans and also has a risk to cause hypersensitivity reaction during the infusion [5, 6]. The patients treated with these initial mAbs could neutralize the effect of the therapeutic antibody because, often displayed anti-mouse immunoglobulins. In order to limit these undesirable effects, the recently developed monoclonal antibodies contain a high proportion of human protein sequence and a less proportion of murine components. The chimeric antibodies are 65% human, humanized antibodies are 95% human, and human antibodies are 100% human.

Small Molecule Inhibitors and Monoclonal Antibodies

These small molecule inhibitors differ from the mAbs in several ways. SMinhs typically interrupt with the cellular processes by interfering with the intracellular signaling of tyrosine kinases (i.e., the enzymes that transfer the phosphate groups from adenosine triphosphate to tyrosine amino acid residues in proteins).Tyrosine kinase signaling induces a molecular cascade that can lead to cell growth, proliferation, angiogenesis and migration in normal as well as malignant tissues. For example HER2/neu, EGFR and VEGF receptors are tyrosine kinases and they are the main target of this targeted therapy [6]. Generally, the SMinhs were administered orally because they are not degraded in the gastrointestinal tract. Moreover, they are manufactured by the chemically process that is less expensive than the bioengineering required for the mAbs. They also achieve less specific targeting than the mAbs, as it is evident in the multitargeting nature of the kinase inhibitors dasatinib, imatinib, sorafenib and sunitinib. In contrat to the mAbs, most of the SMinhs are metabolized by cytochrome P450 enzymes (CYP450), which could result in the interactions with the potent inhibitors of CYP450 such as macrolide antibiotics, warfarin, azole antifungals, protease inhibitors, certain anticonvulsants etc. Most of the SMinhs have short half-lives (few hours) and therefore require daily dosing whereas mAbs have relatively longer half-lives ranging from days to weeks and therefore they are usually administered once every one to four weeks. Imatinib which is one of the first SMinhs is for the treatment of chronic myeloid leukemia (CML) by FDA in 2002. Imatinib acts by inhibiting a constitutive active tyrosine kinase of ABL gene that results from the fusion gene BCR/ABL caused by Philadelphia chromosome (translocation chromosome 9 and 22) [5, 6]. Since this molecular abnormality occurs in almost all the patients with CML, the treatment with imatinib therapy results in a complete hematologic response in 98% of patients. Gefinitib is the second SMinhs FDA-approved which targets the EGFR, has been used successful for the treatment of solid tumors like non-small cell lung cancer (NSCLC). Recently, many others congeners molecules were designed to target EGFR pathway [7].

Indications of Targeted Therapy

The use of targeted therapy has drastically changed the outcomes for some diseases, particularly imatinib has had a dramatic effect on CML whereas rituximab has revolutionized the treatment of non-Hodgkin's lymphoma (NHL); on the other hand, sunitinib has improved the renal cell carcinoma

treatment while trastuzumab has given a high responsiveness for the breast cancer. In other fields, the degree of clinical benefit is more moderate [8]. For example, when erlotinib is added to the standard chemotherapy in the patients with advanced pancreatic cancer there is increase in the survival rate from 17 to 24%, which thereby correlates to an increase in average survival from 24 to 27 weeks. Targeted therapies have provided the option to prolong the survival in patients with definite neoplasms, and for some patients who may not otherwise be treated with anticancer therapy. For example, the elderly patients with NHL and NSCLC, may have comorbidities that can limit the usage of conventional chemotherapy. In such case, the targeted drugs such as rituximab and erlotinib are often less toxic and can be better tolerated than the traditional chemotherapy, thereby, offering these patients an additional treatment options.[8,9] In order to determine the right regimen of dosing and the effectiveness of targeted therapies, the cancer researchers are gradually turning to the pharmacodynamic end points, like levels of circulating tumor a cells, tumor metabolic activity on positron emission tomography (PET) scans, serial levels and the expression of target molecules in tumor tissue, and acquired mutation in cancer cells [9].

Cost of the Targeted Therapy

The targeted therapy has also introduced many new pharmacoeconomic aspects. By the use of oral SMinhs for traditional chemotherapy, some treatment costs get eliminated which even includes those associated with the hospitalization of the patient [10]. However, targeted therapy is mostly used in the combination to traditional chemotherapy. If the targeted therapy includes mAbs then the costs can dramatic increase, for example, for the treatment of the colorectal cancer, the regimen consist of bevacizumab or cetuximab which costs up to $30000 for eight weeks of treatment, as compared with about $60 for fluorouracil based therapy for same number of weeks. Moreover, when the conventional chemotherapy is effective, the reduction in the tumor bulk is anticipated on the serial radiographic studies [11]. On contrary, some of the targeted therapies may impact the clinical benefit by stabilizing the tumors, rather than shrinking them. These considerations increase the complexity and cost to the clinical researchers. Moreover, the repeated biopsies of the tumor tissue could be unacceptable for patients as well as inconvenient to the institutional medical boards. Initially, the clinical studies may increase the time and costs of therapy but they could improve the cost-effectiveness in the long-term by identifying the subset of patients most likely to maximize the benefit from specific drugs [12, 13].

Future Outlook

The various clinical trials of traditional chemotherapeutic agents generally affect the toxicity through the degree of myelosuppression [13]. However, the targeted therapies mostly do not cause a significant hematologic toxicity. The applications for therapeutic dose monitoring (TDM) during the oral targeted therapies may best be reserved for the particular situations such as unexpected or severe toxicities, lack of the therapeutic response, anticipated drug-drug interactions and/or concerns over adherence treatment. The interpatient variability noted with mAbs is similar or lower than that observed with the SMinhs [14]. Few data is available in favour of the TDM procedures with these agents, although the data showed encouraging results with cetuximab, rituximab and bevacizumab. At this time, the TDM of mAbs is not been supported by the scientific proof. However, the targeted therapy has introduced the several new issues for the oncologists and determining the optimal dosing is one challenge [15].

CONCLUSIONS

An effective evaluation of the drug design towards the generation of specific and novel therapies which are focused on the molecular targets related to cancer development may eventually be individualized and personalized to the patient for the maximum efficacy [15]. In order to better define the concentration-effect reports and in order to execute the comparative randomized trials of classic dosing versus pharmacokinetically- guided adaptive dosing a series of remarkable effort should be made [16].

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