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Problems in the development of target-based drugs

Abstract Numerous molecular targets of cancer chemotherapy have been identified based on progress made in molecular biology, and new categories of anticancer drugs have been developed. These include inhibitors for signal transduction, cyclin-dependent kinase, angiogenesis, and matrix metalloproteinase, gene therapy, etc. They are variously called target-based drugs, noncytotoxic drugs, or cytostatic drugs. Such drugs have interesting mechanisms of action and appear promising. However, preclinical and clinical evaluations are difficult. Some drugs have a direct antitumor effect, with demonstrated tumor shrinkage. Others show no direct cytotoxicity. The majority of recent phase I trials have evaluated the maximum tolerated dose, pharmacokinetics, adverse events, and antitumor effect. Unusual, unacceptable toxicities have been noted with some target-based drugs. Few phase I trials or preclinical studies have attempted to demonstrate target inhibition. So far very few studies has shown that there is a correlation between target inhibition and antitumor effect. In general, phase II studies are undertaken with compounds such as trastuzumab which have direct antitumor activity. Phase III trials of most target-based drugs are undertaken immediately after phase I studies since the design of appropriate phase II studies is difficult. The ultimate endpoint of phase III trials of target-based drugs is the same as that for cytotoxic drugs, such as improved cure and survival rates.

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Introduction

Progress in molecular biology has led to the identification of numerous molecular targets of cancer chemotherapy. As a result, many compounds in new categories have been developed to treat advanced malignancies with specific molecular targets. These include inhibitors of signal transduction, cyclin-dependent kinase, angiogenesis, and matrix metalloproteinases, as well as gene therapy, immunotherapy, etc. Drugs in this class are called noncytotoxic drugs, cytostatic drugs, or target-based drugs. The terms are derived from their noncytotoxic or cytostatic characteristics, and these agents are generally considered not to induce tumor shrinkage. However, tumor size depends on the balance between cell division and apoptotic cell death, and some drugs in this class exhibit antitumor activity as demonstrated by decreases in tumor size. Antibodies, tyrosine kinase inhibitors, farnesyl transferase inhibitors, and some forms of gene therapy have been reported to cause tumor shrinkage [1, 2, 4, 8]. At the same time, all anticancer drugs are generally categorized as cytostatic agents, and therefore it would be preferable not to use the word noncytotoxic or cytostatic when referring to this drug category.

Characteristics of target-based drugs

Target-based drugs have specific molecular targets, are believed to be selective in terms of molecular effect, and therefore have minimal toxicity (Table 1). As discussed above, they inhibit tumor growth in the absence of tumor regression and are more effective in patients with a small tumor burden. Chronic dosing and oral administration are recommended for target-based drugs, and

Table 1 Characteristics of and mistaken beliefs about target-based drugs

Affect specific molecular targets
Selective molecular effect
Minimal toxicity and effective at low dose
Tumor growth inhibition in the absence of tumor regression
Radiographic confirmation of inhibition of disease progression possible
Effective in patients with small tumor burden
Chronic dosing and oral administration recommended
Should be combined with surgery, radiotherapy, and chemotherapy

they should be administered in combination with other modalities such as surgery, radiotherapy, and chemotherapy.

The results of preclinical studies and phase I and II clinical trials have demonstrated that some widely held beliefs concerning target-based drugs are not true, however. Some affect many molecular targets, and severe adverse events have been reported with their use [6]. Antitumor antibodies, tyrosine kinase inhibitors, and others show direct antitumor activity, and tumor shrinkage is observed in patients receiving them [1, 4].

Phase I studies

Phase I studies of cytotoxic drugs are carried out to determine dose-limiting toxicities, the maximum tolerated dose (MTD), and recommended dose for phase II trials, evaluate toxicity profiles qualitatively and quantitively, and analyze their pharmacokinetics, pharmacodynamics, and antitumor effect (Table 2) [5]. The majority of target-based drugs do not differ in these parameters, although it is difficult to determine the MTD in some, such as antibodies, because no toxicity is seen even when the dose reaches the biologically active range [6]. The most important but problematic question is how to determine the optimal biological dose (OBD). Surrogate endpoints are required to determine the OBD, although no appropriate methodology has been established to define surrogate endpoints for the majority of target-based drugs. It is extremely rare for phase I trials to evaluate activity against molecular targets. In the past, immune responses such as the T cell subpopulation, phytohemagglutin in blastogenesis, natural killer and killer T cell activities, and macrophage-mediated cytotoxicities were evaluated in immunotherapy. However, these were found to be unreliable. Phase I trials of farnesyl transferase inhibitors have attempted to evaluate the inhibition of farnesyl transferase [1]. Such efforts are essential for the development of target-based drugs.

Table 2 Problems in phase I studies

Unusual or no toxicity
Discordance between surrogate for biological activity and tumor tissue
Meaning of target or therapeutic plasma concentration
Interspecies and -individual differences in protein binding and tumor drug uptake
Degree of interspecies and -individual differences
Use of soft surrogates such as immune response and tumor markers to determine antitumor activity

Numerous problems have been experienced in phase I studies of target-based drugs. While some exhibit no toxicity, the majority exhibit unusual toxicities. Appropriate surrogate endpoints for detection of biological activity have not been established for any target-based agent, and it should be assumed that such surrogates and tumor tissue will show discordant drug effects. When discussing the meaning of the target or therapeutic plasma concentration, interspecies and interindividual differences in drug protein binding and the degree of those differences must be considered. It appears risky to evaluate antitumor activity by "soft" surrogates such as immune response and tumor markers.

Phase II studies

Many controversies remain regarding phase II studies (Table 3). For example, what constitutes an appropriate phase II study? Are they actually necessary? What should the endpoints be? The antitumor activity of conventional cytotoxic drugs is evaluated in nonrandomized trials. The same strategy could be applied if tumor regression was expected from target-based drugs. Agents that are expected to inhibit tumor progression could undergo randomized, controlled phase II studies. In randomized trials, however, soft endpoints such as time to progression (TTP) and/or quality of life could be used to evaluate antitumor activity. Eisenhauer [3] proposed using the disease progression rate instead of the partial response rate, while Von Hoff [7] suggested a 33% improvement in TTP as a possible endpoint. However, the application of these methods would lead to numerous false-positive results.

In the case of matrix metalloprotease inhibitors, phase III trials are being performed in the absence of prior phase II trials. This reflects the difficulty of designing appropriate phase II trials for drugs in this class.

Phase III trials

The endpoints of phase III trials of target-based drugs are the same as for cytotoxic drugs, including cure rate, survival time, TTP, recurrence rate, metastasis, and relief of disease-related symptoms (Table 4). The sample size of trials is determined by the effect of control treatment, magnitude of difference between arms, and α

Table 3 Problems in phase II trials (*TTP* time to progression)

Determining necessity
Appropriate trial design
Low response rates in nonrandomized trials
Soft endpoints (e.g., TTP and quality of life) in randomized trials

Table 4 Questions concerning phase III trials of target-based drugs

How much improvement can be expected from target-based therapy?
How many patients must be enrolled in a trial to obtain statistically meaningful differences?
Are clinical trials of target-based drugs realistic?
Can pharmaceutical companies accept negative results from phase III clinical trials?

and β errors. It is difficult to estimate the improvements in endpoints which can be expected with the use of target-based drugs and how many patients are necessary to achieve statistically significant results. If the expected difference is very small, it is questionable whether the proposed clinical trials are realistic or not. The major question may be whether pharmaceutical companies could accept negative results from phase III trials.

Conclusions

While numerous phase I studies of target-based drugs have been conducted, the target effect has not been evaluated in the majority of clinical phase I trials because methods to detect the specific molecular effect of target-based drugs are lacking. In addition, many phase III studies are being performed without any evidence of antitumor activity. If the results of a majority of phase III studies are negative, this may have an adverse effect on the development of target-based therapies. In the future, cytotoxic drugs will remain an important strategy for cancer treatment. The antitumor activity of cytotoxic drugs is higher than that of target-based ones and it is expected that the tumor selectivity of cytotoxic agents will improve. New molecular targets of cancer chemotherapy will be identified through the study of the mode of action of cytotoxic drugs. Combinations of cytotoxic and target-based drugs may be a possible treatment strategy.

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