Cancer Chemother Pharmacol (2003) 52 (Suppl 1): S97–S101
DOI 10.1007/s00280-003-0596-x

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Strategy for the development of novel anticancer drugs

Published online: 18 June 2003

Abstract Progress in molecular pharmacology has demonstrated each anticancer drug to have a unique molecular target. Recent drug development has focused on compounds that specifically inhibit and/or modify tumor-specific molecular biological changes (target-based drug development). These compounds are generally classified as either small molecules or macromolecules. With the exception of antibodies, the majority of recently developed target-based drugs are small molecules. Assessing the effects of these compounds on their targets would probably help researchers to predict the antitumor effects of these anticancer drugs; however, actually assessing this hypothesis, even in preclinical models, is difficult. Most preclinical experiments attempt to show tumor growth inhibition or shrinkage, leading to a longer survival period or higher cure rate. Few experiments have examined the correlation between antitumor activity and the effect of a compound on its target. In phase I clinical trials of target-based drugs, the determination of maximum tolerated dose is not enough; the effect of the drug on its target should also be evaluated. Recently, dose-escalation strategies based on the effects of drugs on their targets have been proposed, even though an appropriate target effect is necessary but not sufficient to demonstrate clinical efficacy. Compounds that are not specifically directed against molecular targets on or within tumor cells, but against blood vessels, matrix, etc., usually do not cause tumor shrinkage. These compounds include angiogenesis inhibitors and matrix metalloproteinase inhibitors and are usually used in combination with other treatments at the start of clinical trials. Whether the methodology of clinical trials is sensitive enough to detect the subtle effects of these compounds remains uncertain. The effects of experimental drugs on their targets are rarely examined in clinical trials. Few data from translational studies are available and data obtained using surrogate tissues do not necessarily reflect the effects of the drugs on in situ tumors. Parameters such as time to progression, changes in tumor markers, and growth rates often vary significantly and are regarded as soft endpoints. Phase III trials evaluating survival benefit require extensive resources, including a large number of patients, a sophisticated data center, and well-trained study groups. The problems and future prospects of novel anticancer drug development are discussed.

Keywords Target-based drug · Clinical trial · Translational study

This work was presented at the 18th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "New Strategies for Novel Anticancer Drug Development," 8–9 November 2002, Nagoya, Japan.

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Introduction

Many state-of-the-art chemotherapy regimens have been established against each type of solid tumor. Unfortunately, however, the survival benefits of these regimens are negligible; therefore the introduction of more innovative treatment is considered to be essential. To date, treatment has been individualized for patients according to tumor type, histology, and disease stage. As understanding of the molecular basis of cancer cells has increased, biological modification of the natural course of cancer by target-based drugs with or without standard treatment has become a reality. Recently, the individualization of treatment became possible due to pharmacokinetic data based on pharmacogenetic study, molecular biological characteristics, and pharmacogenomic information. Identification of specific molecular features of a tumor has allowed rational drug discoveries to be made and drugs have been screened via modula

tion of specific molecular targets in tumor cells or the tumor environment [8].

Target-based drugs should satisfy the following two conditions. First, they must act by a described mechanism. Second, they must have in vivo antitumor activity, and the former condition must be the explanation for the latter. Many key factors are involved in the multiple steps of growth signal-transduction pathways. To inhibit each step, various strategies are possible; for example, competitors for a ligand or receptor, antibodies against receptors, tyrosine kinase inhibitors, downstream pathway inhibitors such as RAS farnesyl transferase inhibitors (FTIs), mitogen-activated protein (MAP) kinase and mTOR inhibitors, and cell-cycle regulators such as cyclin-dependent kinase (CDK) inhibitors. In addition, apoptosis may also be a significant focus of target-based therapy. Target-based drugs can be classified into small molecules that have specific molecular weights and structural formulas, and macromolecules that include antibodies, gene therapy, cell therapy, immunotherapy, etc. Target-based therapy can also be classified as tumor specific and nonspecific. Tumor-specific target-based therapy modifies tumor-specific molecular change while tumor-nonspecific therapy modifies molecular changes in the tumor environment. For example, matrix metalloproteinase inhibitors, antivascular endothelial growth factor (VEGF) antibody, and VEGF tyrosine kinase inhibitors can be classified as tumor-nonspecific target-based drugs [15, 17, 18].

Clinical trials of target-based drugs

Numerous target-based drugs are under preclinical and clinical investigation. Tables 1 and 2 summarize the status of clinical trials of target-based drugs in Japan. Phase I trials of several drugs have been conducted, although the majority did not progress beyond phase II and/or III trials because of low antitumor effect and/or significant toxicity. Successful compounds include trastuzumab, rituximab, imatinib, and gefitinib (Table 3) [3, 5, 7, 13, 20]. These compounds are antibodies and small molecules. All have an effect on pathways upstream of signal transduction. There are two major factors that influence the successful development of target-based drugs. One of the most important questions is whether the molecules selected as targets are appropriate; are they essential for the growth, invasion, and/or metastasis of the tumor? Another question is whether the clinical trial designs are appropriate; is it possible to demonstrate a survival benefit with a conventional clinical trial? If not, are there any appropriate endpoints for phase III clinical trials?

Clinical development of matrix metalloproteinase inhibitors such as marimastat, prinomastat, and tanomastat has been a complete failure. Matrix metalloproteinase inhibitors against stomach [6], pancreatic [14], ovarian [11], small-cell lung cancer [19], and non-small-cell lung cancer [2, 21], showed no survival advantage compared with standard treatment. Clinical trials of a VEGF tyrosine kinase inhibitor, semaxinib, also failed in advanced colon cancer (Genentech news release, 9 September 2002). Clinical trials of RAS farnesyl transferase inhibitors were also negative against colorectal and pancreatic cancer [4, 22]. In addition, trastuzumab did not improve the survival of patients with non-small-cell lung cancer treated with standard therapy [9]. These failures are explained by inappropriate target selection, inappropriate *go/no-go* decisions for phase III trials, and inappropriate endpoints and target populations in clinical trials.

Table 1 Clinical trials for target-based drugs in Japan: small molecules (*EGFR* epidermal growth factor receptor, *RTK* receptor tyrosine kinase, *PDGFR* platelet-derived growth factor receptor, *VEGF* vascular endothelial growth factor receptor, *FGFR* fibroblast growth factor receptor, *CDK* cyclin-dependent kinase, *PKC* protein kinase C, *CHK-1* checkpoint kinase 1)

Compound	Target(s)	Status
Tyrosine kinase inhibitors		
Gefitinib	EGFR-RTK	Phase I, II[a]
ZD6474	PDGFR, EGFR, VEGFR-RTK	Phase I
Semaxinib	VEGFR-RTK	Phase I[a]
SU6668	VEGFR, PDGFR, FGFR-RTK	Phase I[a]
Imatinib	BCR-ABL tyrosine kinase	Phase I, II[a]
TAK-165	HER2/neu tyrosine kinase	Phase I
CDK inhibitors		
UCN-01	PKC, CDK, CHK-1	Phase I[a]
Flavopiridol	CDK	Phase I
E7070	CDK	Phase I
FTIs		
R115777	RAS farnesyl transferase	Phase I[a]
mTOR inhibitors		
CCI-779	mTOR	Phase I
Binder to tubulin of tumor vessel		
ZD6126	Tubulin of tumor endothelial cell	Phase I

[a]Completed

Table 2 Clinical trials for target-based drugs in Japan: macromolecules (*EGFR* epidermal growth factor receptor)

Compound	Target	Status
Antibody		
Trastuzumab	HER2/neu	Phase I[a]
Rituximab	CD20	Phase I, II[a]
Cetuximab	EGFR	Phase I
Antibody plus drug		
MCC-465	Stomach cancer antigen	Phase I[a]
CMA-672 (calicheamycin)	Acute myeloid leukemia antigen	Phase I
Dendritic cell plus peptide antigen	Prostate antigen Melanoma antigen	Phase I[a] Phase I
Gene therapy	P53 (lung cancer)	Phase I

[a]Completed

Differences in preclinical and clinical evaluation of cytotoxic and target-based drugs

Both cytotoxic and target-based drugs have a molecular target; however, target-based drugs modify specific

Table 3 Positive phase III results of target-based therapy (*AC* doxorubicin, cyclophosphamide, *CHOP*cyclophosphamide, vincristine, doxorubicin, prednisone)

Compound	Conclusion	Reference
Imatinib	Imatinib > interferon plus cytarabine	5
Trastuzumab	AC plus trastuzumab > AC Paclitaxel plus trastuzumab > paclitaxel	20
Rituximab	CHOP plus rituximab > CHOP	3

molecular changes in the tumor itself or tumor environment. Although the screening is target oriented, it is essentially a random screening for the majority of small molecules even in the case of target-based drugs. Therefore the compound inhibits the function of not only a proper target but also other nonspecific biological targets, which obscures the mode of action of target-based drugs. In addition to analyzing toxicity and pharmacokinetics, as well as determining the optimal dose, it is necessary to obtain information regarding antitumor activity in the phase I study of target-based drugs. It is also necessary to analyze the relationship between target inhibition and antitumor effect.

For cytotoxic drugs, tumor shrinkage has been demonstrated to be a surrogate for survival and the evaluation of response rate is the primary endpoint of a phase II study. On the other hand, the purposes of a phase II study of target-based drugs include confirmation of safety and recommended dose, and assessing antitumor response based on changes in tumor size, time to progression (TTP), functional imaging, and monitoring of surrogate markers. To date, no clear primary endpoint of phase II trials has been established except for tumor shrinkage. Trastuzumab, rituximab, imatinib, and gefitinib all demonstrated tumor shrinkage, and they have been made available in Japan through accelerated approval. Even if insight into the antitumor response has not been obtained during single-agent phase I and II trials, *go*/*no-go* decision making is necessary. In the case of *go*, phase I/II combination studies with standard treatment are scheduled. In these trials, the feasibility of combination therapy should be evaluated and better treatment results compared with standard treatment are essential for further comparative studies. The key question remains as to what is the criterion for ''better''?

To make the *go* or *no go* decision for further phase III trials, we need to evaluate the combination therapy data quantitatively. In addition, translational studies are required throughout phase I, II, and I/II trials. In a phase III randomized trial, the endpoints of clinical trials for target-based drugs are prolongation of survival and TTP, and improvement in quality of life to the same extent as cytotoxic drugs. To date, rituximab and trastuzumab have demonstrated survival benefits and improvement in TTP, when added to standard treatment [3, 20]. Imatinib showed a survival benefit compared with standard chemotherapy containing cytarabine and interferon [5]. On the other hand, gefitinib only produced tumor shrinkage in about 20% of patients with prior platinum- and taxane-based chemotherapy [7, 13]. The Iressa Non-small-cell lung cancer Trials Assessing Combination Treatment (INTACT) 1 and 2 demonstrated no survival improvement when gefitinib was added to standard platinum-based chemotherapy in advanced non-small-cell lung cancer without prior chemotherapy [10, 12] (Table 4). These lines of evidence suggest that the decision to go to phase III trial is extremely difficult.

Translational studies of target-based drugs

For the development of molecular target therapy, the role of translational research is rapidly increasing. The whole process from preclinical discovery based on molecular biological evidence to clinical-phase studies is considered to represent translational research [1, 16]. It can simply be defined as the process of determining a treatment solely on the basis of molecular biological characteristics.

Important tasks for the further development of translational research are: creation of the essential infrastructure that takes work from the laboratory to the clinic; development of molecular endpoint assays for clinical material for each target-based drug; and collaborative interaction between clinical and laboratory personnel.

The process for the development of target-based drugs is considered to be translational research. It uses the expression of a particular target as a basis for developing a new agent. For example, the oncogene

Table 4 The results of Iressa Non-small-cell lung cancer Trials Assessing Combination Treatment (INTACT) 1 and 2

	INTACT-1			INTACT-2		
	Gefitinib 500 mg/day	Gefitinib 250 mg/day	Placebo	Gefitinib 500 mg/day	Gefitinib 250 mg/day	Placebo
Complete response (%)	2.1	3.0	0.9	0.6	2.3	1.0
Partial response (%)	47.6	47.2	43.2	31.5	32.7	32.5
Overall response rate (%)	49.7	50.2	44.1	32.1	35.0	33.5
Median survival time (months)	9.92	9.86	11.07	8.74	9.82	9.92
1-year survival (%)	43	41	45	37	41	42
Time to progression (months)	5.55	5.85	5.98	4.67	5.32	5.06

RAS is activated in various malignancies; RAS farnesyl transferase is required for this. FTIs inhibit both enzyme activity and *RAS* activation, resulting in the inhibition of tumor growth. The antitumor activity of FTIs is evaluated in *RAS*-activated tumors, and assays to determine the inhibition of farnesyl transferase have been developed to evaluate the target effect of FTIs. This is precisely the process regarded as an example of translational research.

In the early clinical trials of target-based drugs, evaluation of pharmacokinetic/pharmacodynamic interactions was required. Pharmacokinetic analysis itself can be considered a part of translational research. Modulations of molecular targets, such as enzyme activity, amount of protein, and gene expression, should be evaluated in addition to changes in tumor size and toxicity. Target evaluation before and after treatment is a critical part of translational science. The introduction of several pharmacogenomic techniques has facilitated the measurement of target effect induced by target-based drugs.

Reverse (back) translation and interaction of preclinical and clinical translational studies

Reverse (back) translation is an important concept. Translational study should have two directions, such as preclinical and clinical studies. For example, gefitinib was developed to inhibit epidermal growth factor receptor (EGFR) tyrosine kinase and it showed an antitumor response; however, there is no correlation between EGFR and antitumor response, which means seeking a new molecular target for gefitinib and developing new leads. This process could be considered to be reverse translation.

Tumor shrinkage, TTP, and survival

Many researchers working in the field of molecular target-based therapy stress that clinical trial endpoints should undergo a conceptual revision—from tumor shrinkage to a delay in TTP and improved survival—and that tumor shrinkage is not an appropriate endpoint for the evaluation of target-based drugs. Tumor size depends on the balance of cell division and apoptosis. If a target-based drug induces strong apoptosis, tumor size necessarily decreases. All the molecular target-based drugs already approved in Japan, such as imatinib, gefitinib, trastuzumab, and rituximab, induce strong apoptosis that is reflected by tumor shrinkage and survival.

In patients with stabilized disease (SD) or no change (NC) after treatment, survival is longer than in those patients with progressive disease (PD). If a complete response (CR) or partial response (PR) is achieved, the proportion of patients who experience better than SD/NC increases, which results in better survival. This suggests that tumor shrinkage in clinical trials of molecular target-based drugs is extremely important for improving survival. If the proportion of patients who show better than NC/SD is low, for example 20–30%, and the proportion of patients with PD is 70–80%, it will be impossible to demonstrate a survival benefit. The same problem exists for the evaluation of cytotoxic drugs without tumor shrinkage. It can be said that an agent that does not produce an appreciable objective response cannot be expected to prolong life.

Combination therapy

Imatinib alone showed better survival than standard treatment, i.e. interferon plus cytarabine [5]. With such effective target-based drugs, combination therapy may not be necessary to demonstrate the efficacy of these agents. However, there are two situations where combined use of molecular target-based drugs is appropriate. First, a situation where the effects of target-based drugs are supplemented by those of cytotoxic drugs; and second, the use of target-based drugs as sensitizers to cytotoxic drugs.

Trastuzumab and rituximab were evaluated for efficacy in combination with standard treatment and the combined modality showed a survival benefit compared with standard chemotherapy alone [3, 20]. Even with imatinib, the cure rate may be increased if combined with standard treatment. These three molecular target-based drugs are active by themselves; therefore the combined modalities are a combination of an active target-based drug and active cytotoxic drugs. Gefitinib did not show a survival advantage when combined with standard platinum-based chemotherapy, although the combination was considered to be similar to those containing trastuzumab or rituximab [10, 12].

Molecular target-based drugs can be used as sensitizers to cytotoxic drugs when the target-based drug shows no tumor shrinkage. In this case, the sensitizing effect of the target-based drug should be demonstrated by preclinical studies. However, there is as yet no evidence of a survival benefit in studies based on this rationale. Clinically, the results of combination phase II studies are difficult to evaluate even if the response rates are quite high and survival appears to be promising. There is no gold standard for making the *go*/*no-go* decision.

Summary

Many new molecular target-based drugs have been developed to reverse the malignant process and restore normal cellular behavior. The ultimate goal of treatment with molecular target-based drugs is believed to be improvement in the outcome of survival. Better treatment results are constantly required in cancer therapy in terms of improvements in response rate and survival in different tumor types and to achieve this with acceptable

toxicity. It is extremely important to understand exactly what level of efficacy these target-based drugs have and whether this overlaps or is qualitatively different from the efficacy of conventional treatment. Many molecular target-based drugs have already been evaluated in clinical, randomized phase III trials, and it has become possible to review how these agents have been developed and what the outcomes of these trials have been. Based on this information, we need to draw some conclusions to the various questions to go forward with preclinical and clinical development of molecular target-based drugs and design reasonable and realistic clinical trials. The development of dependable methods to determine which tumors and which patients will respond to these molecular target-based drugs is also required.

Acknowledgements This work was supported by grants-in-aid for scientific research from the Ministry of Education, Science, Sports and Culture, and Ministry of Health, Labour and Welfare, Japan, and an educational grant from Bristol-Myers Squibb.

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