Journal of Human Genetics (2013) 58, 313–316

www.nature.com/jhg

REVIEW

Characteristics of pharmacogenomics/biomarker-guided clinical trials for regulatory approval of anti-cancer drugs in Japan

Akihiro Ishiguro[1], Satomi Yagi[1] and Yoshiaki Uyama[1,2]

Pharmacogenomics (PGx) or biomarker (BM) has the potential to facilitate the development of safer and more effective drugs in terms of their benefit/risk profiles by stratifying population into categories such as responders/non-responders and high-/low-risks to drug-induced serious adverse reactions. In the past decade, practical use of PGx or BM has advanced the field of anti-cancer drug development. To identify the characteristics of the PGx/BM-guided clinical trials for regulatory approval of anti-cancer drugs in Japan, we collected information on design features of 'key trials' in the review reports of anti-cancer drugs that were approved after the implementation of the 'Revised Guideline for the Clinical Evaluation of Anti-cancer drugs' in April 2006. On the basis of the information available on the regulatory review data for the newly approved anti-cancer drugs in Japan, this article aims to explain the limitations and points to consider in the study design of PGx/BM-guided clinical trials.
Journal of Human Genetics (2013) **58,** 313–316; doi:10.1038/jhg.2013.36; published online 9 May 2013

Keywords: biomarker; drug development; international harmonization; pharmacogenomics; PMDA; regulatory science; study design

INTRODUCTION

Pharmacogenomics or biomarker (PGx/BM), is increasingly being utilized in the drug development processes for identifying the appropriate target population of a drug in order to achieve a better benefit/risk balance, and as a consequence it has contributed to effective drug development.[1] Accordingly, in recent years, PGx/BM has been recognized worldwide as an important tool for drug development and it has also been implemented in regulatory reviews.[2]

In oncology, the use of PGx/BM has not only helped in elucidating the underlying molecular mechanism of tumor formation[3] but also contributed to major advances in personalized medicine as novel anti-cancer drugs targeting relevant molecules were successfully developed.[4] As a result, over the last decade more drugs carry PGx/BM information on their labels (prescribing information in Japan).[5] Development of anti-cancer drugs, however, still remains a challenge due to high failure rates in the later stages of clinical development.[6] Several studies indicated that the lack of efficacy is a reason for the attrition mostly seen in the later stages of development.[7–9] In addition, a poor knowledge about the methodology, including the study design in PGx/BM research, is another underlying reason that hampered the translation of PGx/BM technology from the bench to the bedside.[10,11] In this study, in order to identify the characteristics of PGx/BM-guided clinical trials in oncology for regulatory approval of drugs in Japan, we scrutinized the information found under 'key clinical trial' in the new drug applications (NDAs) of anti-cancer drugs that were approved in Japan after April 2006.

MATERIALS AND METHODS

We searched the Pharmaceuticals and Medical Devices Agency (PMDA) website, which is publically available at http://www.info.pmda.go.jp/appro-valSrch/PharmacySrchInit, to identify the NDAs of anti-cancer drugs approved by the Ministry of Health, Labor and Welfare under the category of new molecular entities or new indication after April 1, 2006 on which the guidelines entitled the 'Revised Guideline for the Clinical Evaluation of Anti-cancer drugs'[12] was implemented. In this study, we excluded the NDAs approved for new route of administration, for new dosage and for combination therapy with marketed drug, as well as any NDA that was approved without clinical trial data as a special category based on the notification 'NDAs based on public knowledge'.[13] Accordingly, using 31 December 2012, as the cutoff date, we identified 52 approved NDAs, including 37 new molecular entities and 15 new indications.

To examine the characteristics of PGx/BM-guided clinical trials in oncology for the drug approval in Japan, we focused on the 'key trial', defined as an important clinical trial described in the Pharmaceuticals and Medical Devices Agency review report for each NDA as the key clinical evidence used in evaluating the efficacy and safety of the drug for approval. On the basis of the review reports of 52 NDAs, 108 clinical trials were identified as the key trials. We then classified the key trials whether or not any PGx/BM was used for the drug development. For the analysis, the key trials involving PGx/BM were further classified into three categories as outlined in Figure 1.[14,15] Briefly, the

[1]Pharmaceuticals and Medical Devices Agency (PMDA), Toyko, Japan and [2]Department of Regulatory Science of Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan
Correspondence: Dr A Ishiguro, Office of New Drug V, Pharmaceuticals and Medical Devices Agency, Shin-Kasumigaseki Bldg., 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013, Japan.
E-mail: ishiguro-akihiro@pmda.go.jp
Received 15 March 2013; accepted 11 April 2013; published online 9 May 2013

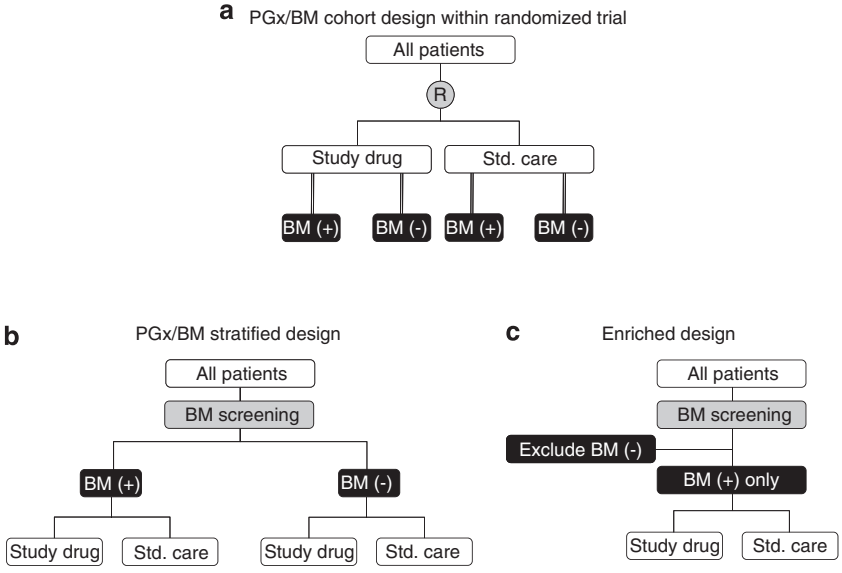

Figure1 Common study designs used in clinical trials utilizing pharmacogenomics (PGx) or biomarker (BM). (**a**) Design where the randomization is independent of the results of the PGx/BM screening. (**b**, **c**) Design where the randomization is performed by the results of the PGx/BM screening. R, randomization; Std. care, standard of care, BM (+), PGx/BM test positive population; BM (−), PGx/BM test negative population.

first category is 'PGx/BM cohort design', where the randomization was independent of the results of the PGx/BM screening. The second and third categories are 'PGx/BM stratified design' and 'enriched design', where the randomization was carried out using the results of the PGx/BM screening. The difference between the second and third categories is whether patients without the target PGx/BM (PGx/BM(-)) were included ('PGx/BM stratified design') or excluded ('Enriched design') in the clinical trial. An orphan status designation, based on the information available in the public database (http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html), was also included as a factor in our analysis, because characteristic differences in the design of clinical trials of orphan and non-orphan drugs (for example, randomization) have been reported previously.[16] The information of the feature in the key trials described above was collected independently by us and differences were reconciled by consensus.

RESULTS

Among the 52 selected NDAs, 29 NDAs (55.8%) contained 58 PGx/BM-guided key trials. Of these 29 NDAs, 8 NDAs also contained key trials without utilizing PGx/BM. Figure 2 shows BMs that were targeted in the PGx/BM-guided key clinical trials and clearly indicates that the epidermal growth factor receptor (EGFR), *Bcr-Abl* and vascular endothelial growth factor were the major targets for drug development in oncology.

Table 1 summarizes the design features of key trials according to the PGx/BM utilization. Fifty-eight PGx/BM-guided trials were classified into 39 'PGx/BM cohort design' and 26 'Enriched design'. Seven trials were classified into both categories because they were enriched based on one BM and another BM was used for conducting the exploratory analysis. In this study, none of the trials could be classified under the 'PGx/BM stratified design' category.

The main objective of the trials with the 'PGx/BM cohort design' was to conduct exploratory analysis on the clinical relevance of the targeted PGx/BM (for example, *Bcr-Abl*, *c-Kit*, EGFR expression, kirsten rat sarcoma viral oncogene homolog (KRAS), β2-microglobulin (MG), phosphatase and tensin homolog deleted from chromosome-10 (PTEN) and vascular endothelial growth factor) in terms of drug efficacy or acquisition of resistance against a drug. Additionally, relationship between the BM (α1-MG, β2-MG and N-acetylglucosaminidase) and drug-induced renal injury was

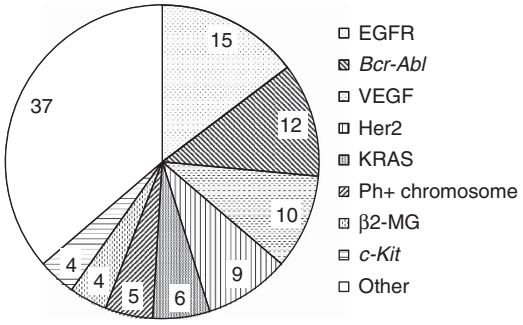

Figure2 Target of pharmacogenomics(PGx)/biomarker(BM)-guided key trials. The numerical value shows number of PGx/BM-guided key trials targeting a particular PGx/BM. In a decreasing order of the number, major BMs targeted in the key trial were epidermal growth factor receptor (EGFR), *Bcr-Abl*, vascular endothelial growth factor (VEGF), human EGFR related 2 (Her2), kirsten rat sarcoma viral oncogene homolog (KRAS), Philadelphia chromosome (Ph+ chromosome), β2-microglobulin (β2-MG) and *c-Kit*. BMs counted <4 were as follows; cluster of differentiation (CD) 20 ($n=3$), echinoderm microtubule associated protein-like 4—anaplastic lymphoma kinase (EML4-ALK), estrogen receptor (ER), extracellular signal-regulated kinase (ERK) and phosphatase and tensin homolog deleted from chromosome-10 (PTEN) ($n=2$), acyl-CoA thioesterase 9 (ACOT9), CC chemokine receptor 4 (CCR4), *c-Met, Crk, Ddx5,* deletion 5q cytogenetic abnormality, deoxycytidine kinase (dCK), excision repair cross-complementing 1 (ERCC1), *FLK31079*, folylpoly-γ-glutamate synthetase (FPGS), *Grb7*, hepatocyte growth factor (HGF), hypoxia inducible factor-1α (HIF-1α), human equilibrative nucleoside transporter (hENT1), insulin-like growth factor receptor 1 (IGF1R), international normalized ratio (INR), multidrug resistance protein 5 (MRP5), *N*-acetylglucosaminidase (NAG), $p95^{HER2}$, phosphoinositide-3-kinase, catalytic, alpha polypeptie (PIK3CA), Ras p21, ribonucleotide reductase M1 (RRM1), thymidylate synthase (TS), von Hippel-Lindau (VHL), α1-MG and γ-glutamyl hydrolase (GGH) ($n=1$).

Table1 Characteristics of key trials of anti-cancer drugs

	Number (%)	
Characteristics	*PGx/BM-guided trial* (n = *58*)	*Trial without PGx/BM use* (n = *50*)
Randomized	35 (60.3)	30 (60.0)
Blinding		
Double-blind	13 (22.4)	13 (26.0)
Single-blind	0	2 (4.0)
Open-label	45 (77.6)	35 (70.0)
Comparator		
Active	21 (36.2)	19 (38.0)
Supportive care	5 (8.6)	0
Placebo	9 (15.5)	11 (22.0)
None	23 (39.7)	20 (40.0)
Primary trial end point reported		
Disease response	30 (51.7)	24 (48.0)
Time to event (survival or disease progression)	28 (48.3)	26 (52.0)
Study design		
PGx/BM cohort	39 (67.2)[a]	—
PGx/BM stratified	0	—
Enriched	26 (44.8)[a]	—
Location		
Japan	15 (25.9)	15 (30.0)
Multi-region including Japan	7 (12.1)	6 (12.0)
Without Japan	36 (62.1)	29 (58.0)
Orphan	21 (36.2)	18 (36.0)
Non-orphan	37 (63.8)	32 (64.0)

Abbreviations: BM, biomarker; PGx, pharmacogenomics.
[a]Seven trials were classified as both of PGx/BM and enriched design.

evaluated in the clinical trials of Azacitidine for the myelodysplastic syndrome. In the randomized clinical trials of Erlotinib for non-small cell lung cancer, EGFR expression level was one of the factors for patient allocation in each arm.[17] In the clinical trials of Gefitinib for non-small cell lung cancer, the efficacy was retrospectively analyzed in stratified population according to types of specific *EGFR* mutations.[18]

The main objective of the trials with 'enriched design' was to stratify the population, which more likely will have a favorable response to a drug. Targeted BMs in the trials under this category were CC chemokine receptor 4, cluster of differentiation 20, deletion 5q cytogenetic abnormality, echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase, EGFR, estrogen receptor, human EGFR related 2 and Philadelphia chromosome. There are probably at least two justifications for the selection of enriched design: approaches involving pharmacological profiling, as well as approaches involving pathological profiling. As for examples we could mention the use of monoclonal antibody against the targeted BM (such as Mogamulizumab, a humanized immunoglobulin G_1 monoclonal antibody against CC chemokine receptor 4 and Cetuximab, a chimeric immunoglobulin G_1 monoclonal antibody against EGFR) for the pharmacological approach, and also the use of low molecular compound against the targeted BM (such as Dasatinib, which inhibits kinases derived from Philadelphia chromosome in acute lymphatic leukemia) for the pathological approach.

Regarding the orphan drug designation, 32.7% (17/52) of the anti-cancer drugs, which included 39 key trials, was designated as orphan drugs. Randomized design was less represented in the key trials for the orphan drugs (14/39, 35.9%) than for the non-orphan drugs (51/69, 73.9%), and the PGx/BM-guided trials showed no clear relationship between the orphan (21/39, 53.8%) and non-orphan drugs (37/69, 53.6%). Disease response as a primary end point was more common in the key trials for the orphan drugs (30/39, 77.0%) than for the non-orphan drugs (24/69, 34.8%).

For the other factors, ~60% of the key trials were conducted as randomized trial, ~70–80% of which were non-blinded trials. Actually, ~40% of the key trials were conducted without any comparator. Time to event was set in about half of the key trials. Only about 25–30% of the key trials were conducted as local trials in Japan and 60% of the key trials were conducted outside of Japan. There were, however, no major differences between the key trials performed with and without the utilization of PGx/BM.

DISCUSSION

This study reveals that the development of nearly half of the approved drugs in oncology was based on PGx/BM-guided trials, suggesting that PGx/BM is commonly utilized in the clinical trials in oncology. The targeted PGx/BM mostly used in the trial was for evaluating the efficacy of a drug, although some BM, such as β2-MG and *N*-acetylglucosaminidase, were used for safety evaluation.

More than half of the PGx/BM-guided key trials were classified as 'PGx/BM cohort design'. Although we commonly found trials also under the 'enriched design' category, no trials were found under the 'PGx/BM stratified design' category. This observation suggests that exploratory application of PGx/BM for evaluating a relationship with drug response (efficacy/safety) is still a major factor in the oncology trials. Although the PGx/BM cohort design is suitable for establishing a hypothesis by analyzing stored samples (for example, DNA), its limitation in data evaluation, such as statistical bias, should be recognized.[5,19] In our recent publication,[5] we have listed five points (such as sample collection for future use and BM qualification) as the remaining challenges in the PGx-guided drug development. To conduct a PGx/BM Cohort study properly, it is very important to consider how to collect samples from clinical trials and store them. Qualification of BM by a regulatory agency is also a key to promote the utilization of PGx/BM in clinical trials in oncology. If more PGx/BM were discovered and qualified, more PGx/BM-guided trials could be conducted. Enriched design may improve an efficiency of drug development by selecting patients who are likely to better respond to a drug, selection of which was based on the response of the candidate PGx/BM to the drug;[14] however, application of this approach has also a limitation because it could not provide a benefit/risk profile in PGx/BM off-target population due to the lack of scientific data. In general, for accumulating strong evidences on the contribution of PGx/BM to drug response, PGx/BM stratified design should be adopted, because this design has been recognized as the gold standard design that could provide evidences for data evaluation.[5,15] Therefore, usefulness and limitation of each design should be thoroughly considered in planning a PGx/BM-guided trial. These data indicate that five challenges described in our recent manuscript are also applicable in oncology.[5]

In this study, orphan designation did not affect the utilization of PGx/BM in the key trial, while drugs designated as the orphan drugs

have been approved on the basis of relatively limited clinical evidence, such as less randomized trials as recently reported.[16,20] To promote drug development in orphan disease, advances in science, such as elucidation of the disease mechanism and discovery/qualification of new PGx/BM in orphan disease, are necessary.[5] Therefore, more research on PGx/BM is encouraged in the case of orphan diseases. In cases where the scientific data on PGx/BM is limited, PGx/BM cohort design may be useful in discovering new hypothesis on the relationship between PGx/BM and drug response. More applications of PGx/BM in clinical trials of orphan diseases may help in identifying a target population and providing more clear evidence on drug responses even in a stratified small population.

As drug development process has become more globalized, data obtained in a foreign country are frequently included in the common technical document used for NDA. Our study shows that ~60% of the key trials are actually conducted outside Japan. Although percentage of trial sites caused no major differences between the key trials performed with and without the use of PGx/BM, more trials involving PGx/BM are needed to be performed in Japan. Recently in Japan, the number of approved drugs, whose approval was based on data obtained from the multi-regional clinical trials (MRCTs), has also increased.[21] Application of PGx/BM in multi-regional clinical trials is encouraged for accumulating more information, for it might contribute to a better understanding about the effects of ethnic factors on drug responses.[5] Furthermore, in recent years, draft guidelines focusing on methodological issues using PGx/BM in clinical trials (such as patient selection and enrichment strategy) have been published independently by the European Medicines Agency and US Food and Drug Administration[22,23] All regulatory agencies (European Medicines Agency, Food and Drug Administration and Pharmaceuticals and Medical Devices Agency) in the international conferences on harmonization (ICH) recognize the importance of PGx/BM in clinical trials and encourage the application of PGx/BM in drug development.[2] For promoting the appropriate application of PGx/BM in clinical trials in the era of globalization, establishment of an international guideline would be important. Thus, regulatory collaborations should be further reinforced.

In conclusion, PGx/BM was commonly utilized in the key trials to provide evidences for regulatory approval of anti-cancer drugs in Japan. However, most of these trials were exploratory rather than confirmatory. More researches, such as discovery/qualification of new BMs, are necessary to further promote the application of PGx/BM in oncology. Common understandings regarding the design of PGx/BM-guided trials, in terms of usefulness and limitation, will contribute to provide better evidences in PGx/BM-guided clinical trials. In the era of globalization of drug development, establishment of an international guideline and close collaboration among regulatory agencies are necessary to promote appropriate application of PGx/BM in clinical trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The views expressed in this article are those of the authors and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.

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