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Pharmacogenetics as Innovative Approach for Phase I Clinical Studies in Cancer Patients

Giuseppe Toffoli*

Experimental and Clinical Pharmacology Unit, CRO-National Cancer Institute, AVIANO, PN, Italy

Editorial

The development of anticancer drugs is expensive due to the high rate of failure of evaluated agents and the duration of this process. Only 1 in 20 cancer drugs entering clinical trials gains regulatory approval: inadequate therapeutic activity and toxicity are the major causes for failure. Drug development is commonly described in "phases" [1]. Phase I trials provide information about safety and aim to define toxicity and maximum tolerated dose (MTD) in patients. While these trials are conventionally conducted in healthy volunteers and include ascending doses, antineoplastic drugs phase I trials involve cancer patients with advanced-stage disease, and not suitable for conventional treatment. This because of the low therapeutic index of antineoplastic drugs (i.e. the ratio between the dose efficacy for the antitumor effect and the dose causing severe toxicity).

Pharmacokinetic (PK) and pharmacodynamic (PD, i.e. toxicity and efficacy) assessments are used to evaluate optimal dose and schedule in phase I trials. Objective response rates within these trials in cancer patients remain low and in some instances does not justify the risk of severe toxicity (earlier analysis of tumor responses in unselected patients recruited to phase I trials indicate a response rate of 3.8%, with a risk of toxic death of 0.54%) [2]. Improvement of phase I clinical trial design, hence, represents a scientific, ethical and financial imperative.

Genetic differences between individuals can affect response to drug treatment. In particular, PK (adsorption, distribution, metabolism and excretion-ADME) is deeply influenced by some genes. Genetic differences concerning PK have been well described for antineoplastic drugs including 6-mercaptopurine and azathioprine with thiopurine methyltransferase (TPMT) [3]; irinotecan with uridyne difosfoglucuronosyl transferase (UGT) [4]; and for several other drugs including warfarin, with CYP2C9 and VKORC1 [5], and abacavir with HLA-B*5701 [6]. These drugs required dose adjustments in high risk patients with a specific genetic profile. Also genetic differences concerning drug target can explain differences in response or toxicity between individuals. The number of cytosine/adenine repeats in the intron 1 of epidermal growth factor receptor (EGFR), can affect the receptor activity and could potentially interfere with the activity of EGFR inhibitors as cetuximab [7].

In most cases, PG suggestions derive from data from postmarketing experience and are performed relatively late in the drug development process. An early discovery of clinically important genomic differences is expected to drive the early development of drugs in the future. In November 2003 FDA realized the first Draft Guidance for Industry Clinical Pharmacogenomics: premarketing evaluation in early phase clinical studies. This guidance was then upgraded in February 2011 [8]. Several pharmaceutical and biotechnology companies have submitted comments to the FDA regarding the voluntary submission process and the procedure for validating exploratory biomarkers. But how forthcoming the firms will be with genomics data still remain to be seen, especially for phase I clinical trials.

The classical design for phase I study does not require genotyping. This procedure is eventually performed during or after the trial in order to investigate genetic association with toxicity. An innovative approach based on stratification of patients on an existing hypothesis, a genetic profile at high risk for toxic adverse event, could improve the outcome of phase I studies. Recently we published a genotype-guided phase I study of irinotecan administered in combination with 5-fluorouracil/leucovorin (FOLFIRI) in advanced colorectal cancer patients. Irinotecan 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin is a topoisomerase I inhibitor, approved world wide for the treatment of metastatic CRC also in association with oxalilatin or antiangiogenetic (i.e. bevacizumab) or EGFR inhibitors (i.e. cetuximab) [9]. Impaired glucuronidation activity of the UGT1A1 enzyme is a predisposing factor to severe irinotecan toxicity, due to a genetic polymorphism of the UGT1A1 gene. UGT1A1*28 is a TA indel polymorphism characterized by an extra TA repeated in the promoter region of the gene [$A(TA)_7TAA$]. This polymorphism is thought to be associated with reduced glucuronidation of SN38, the active metabolite of irinotecan, compared with wild-type UGT1A1 [$A(TA)_6TAA$], leading to variability in the PK of SN38 [4]. Several studies have shown a clear correlation between UGT1A1*28 and severe toxicity of neutropenia [10,11]. The product label for irinotecan in the US has been revised to include UGT1A1*28 as a risk factor of severe neutropenia.

We hypothesize that patients without the UGT1A1*28/*28 (TA_7/TA_7) genotype are less sensitive to the toxic effects of the standard dose of irinotecan, and that higher doses of irinotecan in the FOLFIRI regimen would be tolerated by patients without the risk genotype. Hence, we performed a dose-finding study in patients with the UGT1A1*1/*1 (TA_6/TA_6) and UGT1A1*1/*28 (TA_6/TA_7) genotypes treated with escalated doses of irinotecan. This study defined the MTD of irinotecan used in FOLFIRI (fixed doses of 5-FU 400 mg/m^2 bolus followed by FU 600 mg/m^2 continuous infusion and LV 200 mg/m^2) in heterozygous UGT1A1*1/*28 patients and in homozygous UGT1A1*1/*1 patients. The conclusions of this pharmacogenetic study indicated that the MTD in UGT1A1*1/*28 patients and in UGT1A1*1/*1, was 310 mg/m^2 and 370 mg/m^2, respectively. This increase is almost double compared to the irinotecan dose typically used in FOLFIRI (180 mg/m^2). Moreover, although tumor response was not the primary endpoint of the phase I study, we observed an improved response rate by increasing the irinotecan dose with minimal increases in adverse drug events,

***Corresponding author:** Giuseppe Toffoli, Experimental and Clinical Pharmacology Unit, CRO-National Cancer Institute, AVIANO, PN, Italy, Tel: +39-0434-659612 (659667); Fax: +39-0434-659659; E-mail: gtoffoli@cro.it

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suggestive of increased benefit of administering irinotecan at higher doses [12].

A phase I study design based on genetic profile meets several issues to be considered, in particular the subject enrollment (inclusion/exclusion) for creating homogeneous subgroups of patients, based on their genetic profile, in which to perform dose escalation. The existing hypothesis on which drug dose escalation under investigation in the patients subgroups is based, requires the presence of a strong candidate gene and a validate polymorphism. At present only few genes (TPMT, dihydropyrimidine dehydrogenase (DPD), UGT1A1*28/*6 and CYP 2D6) are recommended for PG analysis in cancer treatment [13]. Alternative approach for patients stratification based on short panel of genes encoding enzymes/transporters instead of a single candidate gene appears even more problematic to perform since the clinical validation of a gene panel is more difficult than a single gene, due to the increased biases. *In vitro* studies of metabolism, transport, or drug targets could help identifying the need for human PG studies, and contribute to the design and analysis of these studies or to define surrogate toxicity/efficacy endpoints.

Most of genetic determinants currently considered for PG study potentially affect PK. Therefore it is important to define the real impact of PK on PD. It must be considered that several observable phenotypes of drug response in human result from the interactions of multiple factors or covariances, including demographic and environmental factors. On this ground genetic differences affecting PK could be easy to detect, but genetic differences affecting PD would be more difficult to recognize. Despite of these limitations, for the phase I studies based on genetic profile it becomes fundamental to determine the relationship between doses, defined by expected blood levels in individuals rather than by administered doses and response (toxicity) and how specific genetic characteristics affect drug doses. Finally, new ethical issues derive from phase I studies designed on genetic profile of patients. Prospective DNA sample collection from patients requires a formal consent from all participants in phase I clinical trials and for retaining DNA in the event that new genomic issues arise after the completion of the studies.

In conclusion, PG represents an innovative tool to improve phase I studies and the application of PG approaches during early drug development represents an evolutionary process. The fundamental difference between the classical trial design is the PG testing. Without stratification of patients based on genotyping the trial may not be powered to detect significant genetic associations related to interindividual variability in drug response. In fact, conventional enrollment of patients for phase I study can occasionally result in over-representation of one genetic group that can introduce bias and decrease power.

Pharmacogenomic markers are now increasingly available, but remain poorly utilized. It is hoped that in future subject selection by genotype during prescreening can be used to ensure adequate enrollment of subjects to create a balanced homogeneous subgroup of population for PK and PD effect of the drug under investigation in phase I studies.

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