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Review

Impact of SLC22A1 and CYP3A5 genotypes on imatinib response in chronic myeloid leukemia: A systematic review and meta-analysis

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ABSTRACT

Contrasting results have been reported on the role of rs628031 and rs683369 polymorphisms of SLC22A1 and rs776746 of CYP3A5 on imatinib treatment response in patients with chronic myeloid leukemia (CML). In the present study, we conducted a systematic review and meta-analysis of published studies to estimate the impact of the above-mentioned gene variants on major molecular response (MMR) or complete cytogenetic response (CCyR) in imatinib-treated CML patients. We performed a comprehensive search through PubMed, Web of Knowledge, and Cochrane databases up to September 2017. The pooled analyses showed association between carriers of SLC22A1 rs628031A allele (GA + AA vs GG, OR: 0.58, 95% CI: 0.38–0.88, P = 0.011) or rs683369G allele (CG + GG vs CC, OR: 0.64, 95% CI: 0.42–0.96, P = 0.032) and a lower MMR rate. The combined analyses also revealed a correlation between the dominant (GG + AG vs AA, OR: 2.43, 95%CI: 1.12–5.27, P = 0.024) or the allelic model (G vs A, OR: 1.72, 95% CI: 1.09–2.72, P = 0.020) of CYP3A5 rs776746 with higher CCyR rates. The subsequent sensitivity analysis confirmed the statistical significance of CYP3A5 rs776746 among Asian CML patients (dominant model OR: 3.90; 95%CI: 2.47–6.14, P < 0.001; allelic model OR: 2.08; 95% CI: 1.47–2.95, P < 0.001). In conclusion, the present meta-analysis supports the association of SLC22A1 and CYP3A5 genotypes with clinical imatinib response rates of CML patients, nevertheless further large studies, particularly in Caucasians, are still warranted to provide conclusive evidences.

Contents

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1. Introduction

The tyrosine kinase inhibitor (TKI) imatinib (IM) mesylate is the gold standard therapy for patients with chronic myeloid leukemia (CML), and inoperable and/or metastatic gastrointestinal stromal tumors (GIST) [1,2]. CML is a myeloproliferative disorder characterized by the genetic translocation t(9;22)(q34;q11.2), encoding the BCR-ABL1 oncogenic fusion protein [3]. BCR-ABL1 kinase inhibition by IM prevents phosphorylation of downstream signaling proteins necessary for CML development [4]. IM has significantly improved clinical response rates and survival outcomes of CML patients, nevertheless about 30% of the treated patients must interrupt IM therapy because of cytogenetic or molecular failure [1]. Although currently there are no pharmacogenetic markers recognized to predict IM efficacy in CML, many studies have been performed, focusing on polymorphisms in genes involved in drug uptake and metabolism [5–8].

The human organic cation transporter 1 (hOCT1), also known as solute carrier family 22 member 1 (SLC22A1), has been proposed as the major uptake transporter for IM [9,10]. Several evidences suggest that variability in hOCT1 expression and its activity play a crucial role on IM treatment response. Indeed, CML patients with low hOCT1 activity showed lower probability of achieving major molecular response (MMR) to IM [11], whereas those with high levels of hOCT1 mRNA exhibit higher rates of complete cytogenetic response (CCyR) or MMR [12–14]. The two non-synonymous polymorphisms in SLC22A1, rs628031 (A1222G, M408V) and rs683369 (C480G, L160F) have been reported to affect respectively IM uptake in CML cell line [15] and IM disposition in CML patients [16]. However, whether rs628031 and/or rs683369 [14,17–20] affect IM treatment responses in CML patients remains a debated issue. On the other hand, IM is metabolized by the microsomal enzyme CYP3A5 [21], whose expression strongly correlates with a polymorphism within intron 3 (6986A > G; CYP3A5*3) [22]. Similarly to SLC22A1 gene variants, contrasting results have been reported on the association between CYP3A5 rs776746 and IM response in CML patients [17,20].

The possible reasons of the conflicting results reported for both polymorphisms in SLC22A1 (rs628031, rs683369) and CYP3A5 (rs776746) on IM treatment responses are still unclear. However, possible explanations may be differences in the criteria used to define IM response and/or small sample size of most studies, limitations that can be overcome by using a meta-analytic approach [23]. In view of this consideration, we carried out a systematic review and meta-analysis of published studies to quantitatively summarize the impact of the above-mentioned polymorphisms in SLC22A1 and CYP3A5 gene, on CCyR and MMR in IM-treated CML patients.

2. Methods

2.1. Search and inclusion/exclusion criteria

The present systematic review was conducted in accordance with the PRISMA Statement principles [24]. PubMed, Web of Knowledge, and Cochrane Library databases were searched up to 27 September 2017 using the Boolean combination of the following key terms: «OCT1 OR hOCT1 OR SLC22A1 OR CYP3A5 OR cytochrome P450 OR cytochrome P-450» AND «SNP OR SNPs OR polymorphism OR polymorphisms OR variant OR variants OR gene» AND «imatinib». Eligible studies were required to meet the following inclusion criteria: (i) investigating the association of SLC22A1 polymorphisms (rs628031, rs683369) and/or CYP3A5 (rs776746) with IM treatment response in CML patients; (ii) reporting information on one of the endpoints of interest (CCyR, MMR) at any time point; (iii) reporting sufficient data for estimating an odds ratio (OR) for the association with the gene variants of interest. Exclusion criteria were: case reports; review articles and editorials; duplication of previous publications; not human studies; not English articles. All potentially relevant studies retrieved in the initial screening step were then read in their entirety to assess appropriateness for inclusion in the systematic review. The reference lists of all included studies and relevant reviews were also checked to identify additional studies missed from the initial electronic search. The corresponding authors were contacted by e-mail when relevant data could not be extracted from the original paper. Studies were excluded if the corresponding author did not answer to the e-mail or was unable to provide the requested data. If two or more studies shared part of the same patient population, the one with the larger sample size was included. All studies were independently analysed by two reviewers (S.C. and S.T.) and any discrepancies in data extraction were resolved through consensus.

2.2. Data extraction and quality assessment

For each primary study included in the qualitative analysis, informative data were collected in a standardized format. Collected information included: first author's last name, publication year, number of patients, country of origin, age, disease phase, IM dosage, response criteria, time of response assessment, genotype counts in responders and non-responders, and the proposed genetic model. The scientific quality of the included studies was evaluated according to the Methodological Index for Non-randomized Studies (MINORS) criteria [25]. MINORS consists of a validated, 12-item scoring tool for non-randomized studies, with a global ideal score of 16 for non-comparative studies and 24 for comparative studies. For each item, the MINORS scale assigns scores as 0 (not reported), 1 (reported but inadequate), and 2 (reported and adequate). The MINORS score was reported as a percentage of the global ideal score. Two reviewers (S.C. and S.T.) independently assessed the quality of each study and disagreements were resolved through consensus.

2.3. Statistical analysis

Deviation of polymorphisms from the Hardy–Weinberg Equilibrium (HWE) was calculated using the Pearson's goodness-of-fit Chi^2 test implemented in the online Finetti's program (available at http://ihg.gsf.de/cgi-bin/hw/hwa1. pl). For each study, the odds