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Cytidine deaminase polymorphism predicts toxicity of gemcitabine-based chemotherapy

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ABSTRACT

Background: The aim of this study was to ascertain whether single nucleotide polymorphisms of cytidine deaminase (*CDA*), a key enzyme in the metabolism pathway of gemcitabine, could predict clinical outcomes of cancer patients with gemcitabine-based chemotherapy.
Methods: We searched MEDLINE and EMBASE up to January 2013 to identify eligible studies. A rigorous quality assessment of eligible studies was conducted according to the Newcastle–Ottawa Quality Assessment Scale. For each included study, the overall survival (OS), overall response rate (ORR) and toxicities were extracted and pooled using random-effects model.
Results: In total, data from 13 studies were included. *CDA* 208A > G and *CDA* 435C > T were not included in quantified synthesis due to limited data. *CDA* 79A > C polymorphism was not significantly associated with OS; however, patients carrying the variant *CDA* 79C allele were likely to have a poor survival, hazard ratio (HR) = 1.03, 95% CI 0.957–1.27 (AC + CC vs. AA). *CDA* 79A > C polymorphism did not correlated with ORR, odds ratio (OR) = 0.719, 95% CI 0.363–1.425 (AC + CC vs. AA). However, patients with the variant *CDA* 79C allele would experience more grade ≥ 3 leucopenia (OR = 2.933, 95% CI 1.357–6.605) and tended to have more severe neutropenia (OR = 1.313, 95% CI 0.157–10.981).
Conclusions: These results suggest that *CDA* 79A > C polymorphisms is a potential biomarker for toxicity of gemcitabine-based chemotherapy and a *CDA* testing before gemcitabine administration is preferred.

1. Introduction

Gemcitabine-based chemotherapy is widely used in various solid tumors (Toschi et al., 2005). Gemcitabine has been recommended as first-line chemotherapy in advanced pancreatic cancer (Burris et al., 1997) and gemcitabine-platinum regimen also provides improved survival compared with other platinum-based chemotherapies in non-small cell lung cancer (NSCLC) (Le Chevalier et al., 2005). However, the clinical response, efficacy and toxicities of gemcitabine-based chemotherapy vary greatly. Pharmacological evidence suggests that genetic variation will affect drug pharmacokinetics and clinical outcomes (Ulrich et al., 2003).

Gemcitabine, a cytidine analogue, is transported into cells through nucleoside transporters, activated by deoxycytidine kinase to form active diphosphorylated and triphosphorylated metabolites, and inactivated by dephosphorylation or deamination. However, 90% of gemcitabine is inactivated by cytidine deaminase (*CDA*) (Wong et al., 2009). There are 17 genes involved in the "gemcitabine metabolism pathway" and 3 functional single nucleotide polymorphisms (SNPs) of *CDA* are mostly investigated (rs2072671, *CDA* 79A > C; rs60369023, *CDA* 208G > A; rs1048977, *CDA* 435C > T). Sugiyama and colleagues (Sugiyama et al., 2007) highlighted the importance of *CDA* polymorphisms for the first time. They reported that carriers of the variant *CDA* 208A allele were associated with lower clearance of gemcitabine and more severe hematological toxicities, compared to those with wild *CDA* 208GG homozygote (Sugiyama et al., 2007). Thereafter, a lot of studies have found that the three functional polymorphisms of *CDA* (*CDA* 79A > C, *CDA* 208G > A, *CDA* 435C > T) are associated with altered pharmacokinetics, enzyme activity and could predict clinical outcomes of gemcitabine-based chemotherapy (Gilbert et al., 2006; Tibaldi et al., 2008, 2012; Okazaki et al., 2010; Joerger et al., 2012a). However, these results were inconsistent or even contradictory, especially for *CDA* 79A > C polymorphism (Tibaldi et al., 2008, 2012; Tanaka et al., 2010; Rodriguez et al., 2011).

The aim of this systematic review was to summarize current published data to ascertain whether *CDA* polymorphisms could predict clinical outcomes of gemcitabine-based chemotherapy.

Abbreviations: *CDA*, cytidine deaminase; OS, overall survival; ORR, overall response rate; HR, hazard ratio; OR, odds ratio; CI, confidence intervals; NSCLC, non-small cell lung cancer; NOS, Newcastle–Ottawa scale; HWE, Hardy–Winberg equilibrium.

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2. Materials and methods

2.1. Searching strategy

This systematic review and meta-analysis was designed and reported in accordance with the PRISMA guidelines (Supplementary information: Table S1. PRISMA Checklist) (Moher et al., 2009). We searched MEDLINE (from January 1966 to January 2013) and EMBASE (from January 1985 to December 2013) to identify published studies and references of appropriate reviews and eligible original studies were also manually screened for additional relevant studies. MEDLINE and EMBASE were searched with a combination of key words of "cytidine deaminase", "single nucleotide polymorphism" and "neoplasm". Medical subheadings and alternative spellings were also considered. There was no language restriction.

2.2. Study identification and inclusion criteria

Two authors (Ding X and Chen W) reviewed all titles, abstracts and full-text articles independently; with discrepancies between two authors solved by assessing the full-text articles and discussion with a third author (Fan H). Records retrieved from MEDLINE and EMBASE were primarily screened by titles and abstracts, and then full-text articles were obtained to further validate the eligibility. References of related papers were also screened with the same process. The inclusion criteria were as follows: 1): prospective or retrospective studies including cancer patients with gemcitabine-based chemotherapy; 2): investigating the relationship between *CDA* polymorphisms and clinical outcomes (response to chemotherapy, survival and toxicities); and 3): detailed data which were reported according to *CDA* genotypes.

2.3. Data extraction and quality assessment

For each eligible study, the following data were extracted: name of first author, year of publication, number of patients, age, percentage of male, ethnicity, cancer types, chemotherapy regimens, genotyping methods, criteria for response to chemotherapy and toxicities, frequencies of *CDA* genotype, allele frequencies, overall survival (OS), number of good response and poor response, and number of patients with severe toxicities. Ethnicity was simply classified as Asian, Caucasian or mixed. For OS, Cox proportional hazard ration (HR) and 95% confidence intervals (CIs) were collected. Two authors (Ding X and Chen W) extracted data independently with a predesigned data collection form and they reached consensus on each item. Methodological quality of included studies was assessed with the Newcastle–Ottawa scale (NOS) (Wells et al.) for cohort studies, which evaluates 3 aspects of a cohort study: selection, comparability and outcome. The NOS identifies high quality with a star and there are a maximum of 4 stars, 2 stars and 3 stars in the "selection", "comparability" and "outcome", respectively. Also, quality assessment was performed by two authors (Ding X and Chen W) independently.

2.4. Definition of endpoints

The primary endpoints of this systematic review were response to chemotherapy and overall survival and secondary endpoints were toxicities. Response to chemotherapy was assessed with RECIST criteria (Therasse et al., 2000), while "good response" was defined as complete response + partial response and "poor response" was stable disease + progressive disease. Data of overall survival and survival time were extracted from studies directly according to studies' own definition. Toxicities were assessed using the National Cancer Institute Terminology Criteria for Adverse Events version 3.0 and grade ≥ 3 toxicities were classified as severe toxicities.

2.5. Statistical analysis

For studies reporting detailed genotype data of *CDA* polymorphisms, allele frequencies were calculated as well as the distribution of Hardy–Winberg equilibrium (HWE) with chi-square test for goodness of fit. And a $p < 0.05$ indicated disagreement with HWE. Due to limited data about *CDA* 208G > A and 435C > T polymorphisms, quantitative synthesis was performed for *CDA* 79A > C polymorphism only. The association strength of *CDA* 79A > C polymorphism with response was estimated with odds ratio (OR) and 95% CIs in 4 comparison model (homozygote comparison [CC vs. AA], heterozygote comparison [CA vs. AA], dominant model [CC + CA vs. AA] and recessive model [CC vs. CA + AA], assuming the dominant and recessive effect of the C allele, respectively). The pooled HR and 95% CIs were calculated with HRs and 95% CIs from eligible studies (only HR in dominant model [CC + CA vs. AA] was available for quantitative synthesis). The correlation between *CDA* polymorphism and severe toxicities were estimated with pooled ORs and 95% CIs in dominant model (CC + CA vs. AA).

Heterogeneity between studies was detected using chi-square by Q test, and a p value less than 0.1 was considered significant (Lau et al., 1997). Data from individual studies were all pooled using random-effects model (based on DerSimonian–Laird method). Publication bias was detected via Begg's test and the Egger' linear regression test, and a $p < 0.05$ was considered significant (Egger et al., 1997). All statistical analyses were calculated with STATA software (version 10.0; StataCorp, College Station, Texas USA). And all p values are two-sided.

3. Results

3.1. Selection of studies

A total of 623 records were identified by our searching strategy. After primary screening of titles and abstracts, 56 potentially relevant records were further reviewed by retrieval of full-text articles. As a result, 13 (Tibaldi et al., 2008, 2012; Soo et al., 2009; Okazaki et al., 2010; Tanaka et al., 2010; Rodriguez et al., 2011; Erculj et al., 2012; Farrell et al., 2012; Joerger et al., 2012a,2012b; Kasuya et al., 2012; Li et al., 2012; Xu et al., 2012) eligible studies were identified and included in quantitative synthesis. The process of selection was shown in Fig. 1.

3.2. Characteristics of eligible studies

Characteristics of the 13 eligible studies (Tibaldi et al., 2008, 2012; Soo et al., 2009; Okazaki et al., 2010; Tanaka et al., 2010; Rodriguez

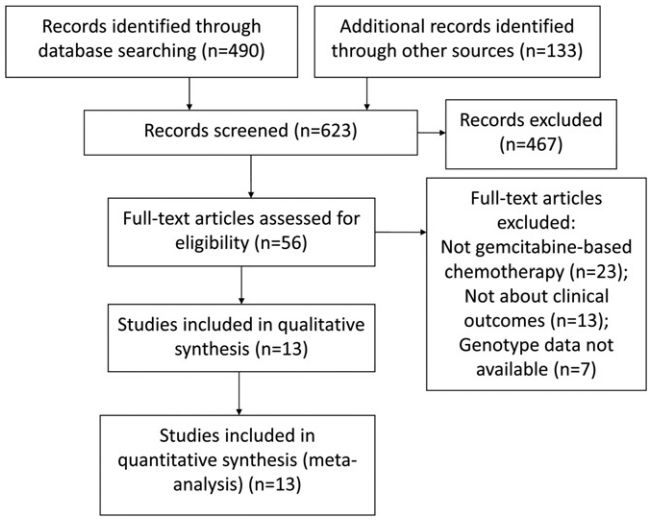

Fig. 1. Flow diagram for study selection.