Author’s response to reviews

Title: Evaluation of the impact of single-nucleotide polymorphisms on treatment response, survival and toxicity with cytarabine and anthracyclines in patients with acute myeloid leukaemia: A systematic review protocol

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Version: 1 Date: 27 Mar 2019

Author’s response to reviews:

1. In your section on Risk of Bias of individual studies, you state that "the methodological quality will be evaluated according to the GRADE protocol". GRADE is not a tool or framework for assessing the methodical quality of individuals studies, it is a tool/framework for assessing the certainty of evidence across studies. Please revise this accordingly.

Answer: First, I would like to thank all the comments. They were essential for the improvement and enrichment of the project. The GRADE of this protocol topic was withdrawn.

2. The section labeled Data Synthesis mixes two concepts: the synthesis of the data and the assessment of the certainty of the evidence. RevMan cannot be used to estimate the "leave of evidence in high, moderate, low and very low, according to GRADE". RevMan can produced pooled estimates of effect, although i will be surprised if your studies are sufficiently homogeneous to support statistical pooling. So you need to dis-entangle these two concepts, and have two sections, one titled Data Synthesis and the other titled Risk of Bias Across Studies (or something similar).
Answer: The initial paragraph referring to the REVMEN was withdrawn, keeping it only for the evaluation of the significance level. In addition, the form was adjusted for the analysis. It was also better explained how GRADE protocol will be used here.

P11, L2: “The authors will consider whether to perform a meta-analysis on the impact of each SNP on treatment with cytarabine and anthracyclines regarding each outcome for this review.”

P11, L10: “Homogeneity for clinical and statistical questions will be considered in deciding whether a meta-analysis is performed. For this, data extraction and effect size estimation will be performed for each prognostic outcome and each SNP, which include continuous (e.g., the means and standard errors for the mean in exposed and non-exposed groups or the mean difference between groups) or categorical effect measure (e.g., the overall event rate of a time-to-event outcome across the whole study period or hazard ratio). Adjusted effect measures will be preferred over unadjusted measured. A review on the performance of a certain prognostic model would extract measures such as discrimination (c-statistic) and calibration (calibration slope, OE ratio) and, if applicable, reclassification (NRI), net benefit measures, etc. For predictive/treatment selection factor studies, the key statistic to extract will be the treatment-covariate interaction estimate; that is, the estimated difference in treatment effect according to changes in a particular predictor (covariate). Formulae for continuous (mean difference) and categorical (relative risk) outcomes will be applied to estimate the effect size (and 95% confidence interval (95% CI)) using Review Manager. If there is insufficient information to perform effect-size calculations, the mean values and/or standard deviations will be requested from the authors of the original studies. Variability in the effect of the interventions will be tested for statistical heterogeneity using the chi-square (χ2) test with the corresponding p-value (Cochrane test) and I² statistic. Heterogeneity will be considered low if I² ≤ 50%. The level of significance will be set at 5%, and all analyses will be performed in RevMan. For low heterogeneity, a fixed-effect meta-analysis will be used to estimate the treatment effect; for high heterogeneity, we will use a random-effects model.”

P12, L6: “The certainty of evidence across studies will be evaluated according to the GRADE protocol (41-43) for each outcome considering each SNP. We will estimate the evidence level according to Grades of Recommendation, Assessment, and Development and Evaluation (42). This tool allows for the definition of four evidence levels (high, moderate, low or very low). The study design is the starting point in assessing the quality of evidence for each outcome. Randomized controlled trials are designated with the highest level of evidence because they are considered to be less prone to methodological limitations. Observational studies will be initially considered to provide the lowest level of evidence because they have greater methodological limitations. There are five possible factors that subsequently diminish study quality: risk of bias (or methodological limitations), inconsistency, imprecision, indirect evidence and publication bias (34).”
3. You will need to re-do your PRISMA-P checklist after doing this.
Answer: The document addional_file1_PRISMAP_Check_list has been corrected.

Reviewer reports:

Major revisions

Rather than saying "standard chemotherapy" you should refine the topic to indicate the drugs you considered.

Answer: The drugs chosen are protocol for our country's public health system, not for every patient. We made term's modifications.

Title: Evaluation of the impact of single-nucleotide polymorphisms on treatment response, survival and toxicity with cytarabine and anthracyclines in patients with acute myeloid leukaemia: A systematic review protocol.

P5, L16: “... (b) when participants who have undergone or are undergoing cytarabine- and anthracycline-associated (11, 14) or isolated cytarabine chemotherapy ...”

P5, L24: “...In AML, there are several SNPs, but not all of them are related to the metabolism of cytarabine and anthracyclines ...”

P6, L8: “The descriptions of all genes and their SNPs were initially evaluated on the PharmGKB database to assess whether they are related to cytarabine and anthracycline metabolism (daunorubicin or idarubicin) ...”

P7, L12: “...: containing at least one group evaluating the SNPs studied, assessing how these SNPs modify the metabolism of cytarabine and anthracyclines or how SNPs affect the outcomes of interest, and using at least cytarabine in all arms...”

P11, L2: “...The authors will consider whether to perform a meta-analysis on the impact of each SNP on treatment with cytarabine and anthracyclines regarding each outcome for this review.”

In the abstract please mention the reason for excluding FAB type 3

Answer: P2, L18“Studies that include patients with promyelocitic leukemia (FAB type 3) will be excluded, since it betokens a worse prognosis.”
P6, L20, What is an appreciable frequency? This obviously depends on the NGS platform used. However you should have some idea about how low of a frequency you can reliably accept.

Answer: The writing was incorrect, and adjustments were made for improvement.

P5, L26: “Single-nucleotide polymorphism is a type of polymorphism characterized by a single-nucleotide variation in a genetic sequence occurring in a minimum of one population.”

Please do not use past tense in methods section

Answer: It is in the past sentence because this evaluation was made before the beginning of the protocol to select the SNP's to be studied.

It seems that you have already selected the genes from a database; you need to explain what this database is and how is it curated. Who enters data in to it? Is it industry sponsored ? Most people will not have time to follow the link and find out for themselves. How can you be sure that all relevant genes are included?

Answer: PharmGKB® is a registered trademark of HHS and is financially supported by NIH/NIGMS. It is managed at Stanford University (R24 GM61374). The PharmGKB is a pharmacogenomics knowledge resource that encompasses clinical information including clinical guidelines and drug labels, potentially clinically actionable gene-drug associations and genotype-phenotype relationships. PharmGKB collects, curates and disseminates knowledge about the impact of human genetic variation on drug responses through the following activities: Annotate genetic variants and gene-drug-disease relationships via literature review; Summarize important pharmacogenomic genes, associations between genetic variants and drugs, and drug pathways; Curate FDA drug labels containing pharmacogenomic information; Enable consortia examining important questions in pharmacogenomics; Curate and participate in writing pharmacogenomic-based drug dosing guidelines; Contribute to clinical implementation projects for pharmacogenomics through collaborations; Publish pharmacogenomic-based drug dosing guidelines, very important pharmacogene summaries and drug-centered pathways; Display all information on the website and provide comprehensive downloads.

It’s a partner the Clinical Pharmacogenetics Implementation Consortium (CPIC®), a Pharmacogenomics Research Network (PGRN), a precision FDA and a PharmCAT. The Clinical Pharmacogenetics Implementation Consortium (CPIC®) is an international consortium of individual volunteers and a small-dedicated staff who are interested in facilitating use of pharmacogenetic tests for patient care. CPIC started as a shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN) in 2009. CPIC guidelines are indexed in
PubMed as clinical guidelines, endorsed by ASHP and ASCPT, and referenced in ClinGen and PharmGKB.

In the protocol:

P4, L15: “There is a database registered under HHS and financially supported by NIH/NIGMS. This database collects, curates and disseminates data on the impact of genetic variations in humans on drug responses. This registry was made by annotating genetic variants and gene-drug-disease relationships via literature review and summarizing important pharmacogenomic data and associations between genetic variants and drugs, and drug pathways, among others (26).

However, the findings in the literature are still insufficient regarding the evaluation of the level of evidence and the risk of bias in studies that address this issue. In addition, there is no other similar review under development registered at PROSPERO (32). Therefore, a study that fills these gaps will be important to translate the results into recommendations for clinical practice based on reliable evidence (15, 26).”

P6, L29: “PharmGKB® is a registered under HHS and is financially supported by NIH/NIGMS. It is managed at Stanford University (R24 GM61374). It has Clinical Pharmacogenetics Implementation Consortium (CPIC®), Pharmacogenomics Research Network (PGRN), precisionFDA and PharmCAT as partners. Clinical Pharmacogenetics Implementation Consortium (CPIC®) started as a shared project between PharmGKB and Pharmacogenomics Research Network (PGRN) in 2009. CPIC guidelines are indexed in PubMed as clinical guidelines and referenced in ClinGen and PharmGKB (26).”

It is useful to indicate at least what subgroups you have in mind at this stage

Resposta: P11, L2: “The authors will consider whether to perform a meta-analysis on the impact of each SNP on treatment with cytarabine and anthracyclines regarding each outcome for this review…”

Minor revisions

The quality if written English needs to improve. I have mentioned a few below but I stopped picking them up after the introduction as there are so many. Please get this proofread and edited
by a native English speaker. I suggest to write in short sentences rather than in convoluted long sentences.

For example the wording in page 3 L12-14 is grammatically incorrect and can be split in to 2-3 short sentences.

Answer: All long sentences have been reevaluated. In addition, we have submitted the manuscript for American Journal Experts reviewing.

P4L1: "that carries the Ara-C transport "; this is unclear

P4L3: "metabolize Ara-C in cytarabine monophosphate " Ara-C to cytarabine monophosphate ?

Answer: P3, L21“Subsequently, the DCK gene (20) encodes the enzyme that catalyses the rate-limiting first phosphorylation step in the activation of cytarabine to cytarabine monophosphate (Ara-CMP).”

P4 L10-12:"anthracyclines is carried out in several tissues, also initiating in the cellular membrane, being able to be realized by several types... " the wording here is unclear

May be it is more useful to highlight the metabolism of these drugs in diagram rather than describing in text.

Answer: For a better understanding we have reduce the sentences’ size.

P4L18: "....drugs present SNPs" ; better to say "....drugs have SNPs". This is the first place you use the abbreviation SNPs and you need to expand it here

Answer: The first time the term was used was on P3, L13: “...Thus, the study of genetic alterations related to the appearance of AML, such as somatic mutations and simple nucleotide polymorphisms (SNPs)…”

P5, L15-20; Please make this paragraph succinct. Also in the paragraph before, there is no need to explain what level of evidence is

P12L21-24; There is no need to explain what GRADE is

Answer: Done
P13 L1-3: It is unclear what the authors mean here

P13 L5-6: "Studies with insufficient data for the meta-analysis will be maintained in the systematic review"; what does this mean?

Answer: modified.

P14 L9: What is LMA? is it AML?

Answer: Yes, it was corrected.