Integrating pharmacogenomic and pharmacometabolomic data towards personalized opioid therapies for cancer pain

Advanced cancer patients usually receive opioid therapy for pain (1). Unfortunately, some patients did not benefit from the analgesic treatment and/or experience side effects such as nausea and vomiting (2,3). Pharmacogenetic studies have suggested that this interindividual variability in response is due to genetic variations in genes involved in opioid action or metabolism, but so far these data are not robust enough to support the development of clinical guidelines for personalized opioid therapy (reviewed in 4).

We believe that new integrated omic approaches are needed to identify novel and useful markers for opioid response and side effect occurrence. The objective of this project is to combine genome-wide genotyping and metabolic data, using machine learning algorithms, to identify clinically relevant markers for the tailored opioid treatment of cancer patients.

In collaboration with the Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy), the European Pharmacogenetic Opioid Study (EPOS) and CERP study (NCT01809106) groups, we already recruited ~2000 patients treated with opioids for cancer and we are continuing the recruitment (total planned number of patients = 2300). We will calculate, for each patient, the average of pain intensity differences (APID) between baseline and each follow-up assessment, whenever possible, as a measure of their opioid response (alternatively we will consider the pain relief score, for patients recruited in a previous cross-sectional study), and a composite nausea-vomiting score (NVS).

We will genotype >900,000 genetic variants using Axiom Precision Medicine Research Arrays, in the whole patient series. We will identify genetic variations associated with pain relief or with nausea-vomiting by logistic or linear regression. We will also calculate polygenic scores for the opioid response and toxicity phenotypes.

We will metabolically profile the serum of 200 newly recruited patients, using mass spectrometry coupled with liquid chromatography. Using partial least squares-discriminant analysis, we will compare the metabolic profiles (metabolomes) between opioid responders and non-responders (defined on the basis of their APID or pain relief scores) and between patients with high NVS and low NVS. These analyses will identify metabolites associated with opioid efficacy and toxicity. Due to the relatively small patient series that will be profiled, this pharmacometabolomic study should be considered a pilot study.

We will apply machine learning methods to identify significant SNP-SNP interactions associated with opioid efficacy and toxicity. We will identify SNPs associated with different metabolite levels in responders vs. non-responders and in patients with high vs. low NVS. We will also identify metabolite combinations classifying responders to opioids and patients that will develop opioid-related toxicity.

With this project, we expect to set the foundation for the pharmacogenomics and pharmacometabolomics of opioid therapy in cancer patients. Moreover, we expect to identify new genetic and metabolic markers, or combinations of them, explaining the inter-individual variability in opioid response (in terms of efficacy and toxicity). Thus, our final goal is providing new tools for the personalized management of advanced cancer patients receiving opioid analgesia, with the aim of improving their quality of life.

References:


**Keywords**: SNP, GWAS, drug response

**Contacts**: francesca.colombo@itb.cnr.it

**Website(s)**:

**Authors**: Francesca Colombo (ITB), Alex Graudenzi (IBFM), Daniela Gaglio (IBFM)