A case–control study to evaluate the risk of agranulocytosis and neutropenia associated with the concomitant use of metamizole and fluoropyrimidine and oxaliplatin-based chemotherapy

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000000933

Study ID

1000000933

DARWIN EU® study

No

Study countries

☐ Spain

Study description

This is an observational, retrospective, multicentre case–control study. All necessary information will be collected from the electronic health records of patients treated with fluoropyrimidines and oxaliplatin.
The study will include patients diagnosed with different neoplasms who have received chemotherapy with fluoropyrimidines and oxaliplatin, prescribed by medical oncology services.

Study status

Ongoing

Research institutions and networks

Institutions

Puerta de Hierro-Majadahonda University Hospital

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Institution

Contact details

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 09/02/2026

Actual: 09/02/2026

Study start date

Planned: 02/02/2026

Actual: 10/02/2026

Date of final study report

Planned: 30/09/2026

Sources of funding

- No external funding

Study protocol

PROTOCOLO METAMIZOL - 13_01_26.pdf (254.57 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Primary data collection

Study design:

This is an observational, retrospective, multicentre case–control study. All necessary information will be collected from the electronic health records of patients treated with fluoropyrimidines and oxaliplatin

Main study objective:

To quantify and characterise the risk of neutropenia associated with the use of metamizole in patients treated with fluoropyrimidine- and oxaliplatin-based chemotherapy

Study Design

Non-interventional study design

Case-control

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

CAPECITABINE

OXALIPLATIN

FLUOROURACIL

LEVOLEUCOVORIN

METAMIZOLE

Anatomical Therapeutic Chemical (ATC) code

(L01BC06) capecitabine

capecitabine

Medical condition to be studied

Agranulocytosis

Neutropenia

Febrile neutropenia

Population studied

Short description of the study population

The study population will comprise adult patients with a diagnosis of cancer who received first-line chemotherapy with fluoropyrimidine- and oxaliplatin-based regimens (FOLFOX or CAPEOX/XELOX). Eligible patients must have completed at least one full cycle of chemotherapy and have available blood test results both prior to treatment initiation and during or at the end of the first chemotherapy cycle.

Patients treated with multi-agent chemotherapy regimens including three or more agents other than fluoropyrimidines and/or oxaliplatin, those receiving second-line or subsequent treatments, those treated concomitantly with radiotherapy, and patients with pre-existing neutropenia (absolute neutrophil count <1,500/mm³) before the first chemotherapy cycle will be excluded.

Age groups

- Adults (18 to < 65 years)
  - Adults (18 to < 46 years)
  - Adults (46 to < 65 years)
- Elderly (≥ 65 years)
  - Adults (65 to < 75 years)
  - Adults (75 to < 85 years)
  - Adults (85 years and over)

Special population of interest

Immunocompromised

Estimated number of subjects

603

Study design details

Setting

The study will include patients diagnosed with different neoplasms who have received chemotherapy with fluoropyrimidines and oxaliplatin, prescribed by medical oncology services

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Comparators

For the analysis of the primary outcome, the following operational definitions will be established to ensure the identification of incident events and temporal comparability between cases and controls.

Case: a patient who, after initiation of chemotherapy and during the follow-up period, experiences a first incident episode of neutropenia, defined as an absolute neutrophil count (ANC) <1,500/mm³ (<1.5×10⁹/L), documented in a laboratory test.

To be considered an incident episode, the patient must have at least one prior laboratory determination with an ANC ≥1,500/mm³.

The index date for cases will be the date of the laboratory test in which neutropenia is first documented.

Control: a patient from the same source population who, having initiated chemotherapy and remaining under laboratory follow-up, has not developed neutropenia up to the assigned index date.

Each control will be assigned an index date corresponding to a laboratory determination at an equivalent time point in treatment (same chemotherapy cycle number or, if not available, the closest laboratory assessment), ensuring that the control is “at risk” at that time.

Outcomes

Outcome data will be collected from available laboratory and clinical information recorded in the electronic health records of included patients, from the start of treatment until one month after completion of first-line

chemotherapy.
The primary outcome will be the occurrence of neutropenia, defined as the presence of an absolute neutrophil count (ANC) <1,500/mm³ (<1.5×10⁹/L) in any laboratory determination performed during follow-up. For analytical purposes, only the first incident episode of neutropenia occurring after initiation of chemotherapy will be considered. The index date will correspond to the date of the laboratory test in which this episode is first documented.

Secondary outcomes:

Febrile neutropenia: its occurrence will be recorded according to commonly accepted clinical criteria and, when documented in the medical record, will be coded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 6.0:
Grade 3: neutrophil count <1,000/mm³ with a single temperature >38.3°C or a sustained temperature >38.0°C for more than one hour
Grade 4: life-threatening consequences requiring urgent intervention
Grade 5: death

Agranulocytosis: defined as an absolute neutrophil count <500/mm³ (<0.5×10⁹/L)

Modification of the chemotherapy regimen:
Dose reduction
Treatment discontinuation
Treatment delay

For each primary and secondary outcome, the date of occurrence and the number of chemotherapy cycles received at that time will be recorded.

For all outcome variables, events must occur within the predefined observation period, from the initiation of chemotherapy to one month after its completion. Only one event per patient will be considered in the analysis, in order to avoid the influence of recurrent episodes.

Data analysis plan

Descriptive analyses:

A descriptive analysis will be performed for all study variables, using appropriate summary measures according to the nature of each variable: Continuous variables will be presented as mean, range and standard deviation. Categorical variables will be presented as percentages of the column total and the number of observations in each category, both by study group and overall. Ordinal variables with a small number of categories (fewer than 10) will be described using two tables: one presenting descriptive statistics as continuous variables (when meaningful) and another presenting categorical distributions. Ordinal variables with more than 10 categories will be analysed using the same approach as continuous variable.

Inferencial analyses:

he association between exposure to metamizole and the occurrence of neutropenia will be estimated by calculating OR and their corresponding 95% confidence intervals (95% CI).

In the crude analysis, the OR for exposure to metamizole will be calculated by comparing cases (first incident episode of neutropenia) with controls (no neutropenia during the risk period).

In the adjusted analysis, a multivariable logistic regression model will be used, with case/control status as the dependent variable and exposure to metamizole as the main independent variable, according to the prespecified definition of ‘recent use’. The model will be adjusted for prespecified potential confounders, including demographic variables (age and sex), type of chemotherapy received

(FOLFOX vs CAPEOX), baseline renal function (presence of chronic kidney disease or estimated glomerular filtration rate), baseline haematological status (haemoglobin, total leukocyte count and platelet count), number of chemotherapy cycles received, prior radiotherapy, use of granulocyte colony-stimulating factor (G-CSF), and concomitant use of other medications with potential myelotoxic effects.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

Electronic health records

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No