Observational study on the incidence of infections in patients with relapsed/refractory FLT3+ acute myeloid leukemia treated with Gilteritinib
SEIFEM-GilteRInf 2022 (Gilteritinib Related Infections) Study.

Background and study rationale

Acute myeloid leukemia (AML) patients with refractory or relapsed (R/R) disease after induction chemotherapy have a poor prognosis with standard chemotherapy [1]. The prognosis may be further aggravated by the susceptibility to infection of this category of patients often due to persistent neutropenia [2][3].
Activating mutations of FMS-like tyrosine kinase 3 (FLT3) are observed in approximately 30 percent of AML cases [4] mainly as in-frame internal tandem duplications (ITDs) within the juxtamembrane region of the protein or as missense point mutations in the tyrosine kinase domain (TKD). FLT3 is expressed in early hematopoietic stem and progenitor cells and regulates their proliferation and differentiation. In patients with AML, the presence of the FLT3 mutation negatively affects survival, both at diagnosis and upon failure of initial therapy [5].
Over the years, several FLT3 inhibitors, currently in development or approved for the treatment of AML, have been devised and vary in kinase selectivity, potency, and clinical activity.
Gilteritinib, is a novel selective tyrosine kinase inhibitor (TKI) that acts by showing greater specificity for FLT3 and higher potency than the first generation of TKIs, competitively inhibits the ATP-binding site of FLT3 receptors, leading to inhibition of receptor signaling and thus cell cycle disruption.
Its approval by the Food and Drug Administration, with indication for FLT3-positive R/R LMA (FLT3+), is based on the results of the phase 3 ADMIRAL study, which demonstrated its superiority over chemotherapy in this setting [6].
In the study, with a median follow-up of 17.8 months, median Overall Survival (OS) was significantly longer (by 3.7 months) in the Gilteritinib arm than in the salvage chemotherapy arm.
OS rates at 12, 18 and 24 months in patients receiving Gilteritinib were 37%, 27% and 20%, respectively (compared with 19%, 15% and 14% in the comparison arm).

Febrile neutropenia was the most common grade □ 3 adverse event in the Gilteritinib arm (45.9%), with pneumonia and septic shock the most common fatal adverse events (1.2% and 0.8% of cases, respectively) [7].
In view of recent approval (FDA 2018, EMA 2019), there is a lack of real-life experience in the literature on the management and outcome of infectious issues, which could be significant given the frailty of the patients for whom Gilteritinib is intended.
We also know that Gilteritinib is mainly metabolized through CYP3A4, so there is a recommendation in the data sheet to avoid concomitant use of strong CYP3A4 inducers. The phase I/II CHRYSALIS study [8], which evaluated potential interactions between Gilteritinib and moderate and strong CYP3A4 inhibitors (e.g., some antifungals such as fluconazole, voriconazole, and posaconazole and some antibiotics such as clarithromycin, erythromycin, and azithromycin), demonstrated a less than 2-fold increase in exposure to Gilteritinib with concomitant administration of a strong CYP3A4 inhibitor. However, this increase was not considered
clinically significant because the incidence of AEs did not differ in the two groups.
In a drug-drug interaction study, the effects of moderate CYP3A4 inhibitors (e.g., fluconazole) and strong CYP3A4 inhibitors (e.g., itraconazole) on the pharmacokinetics of Gilteritinib were evaluated.

The results showed that itraconazole was associated with a significant increase in systemic exposure of Gilteritinib (~2.3-fold), while fluconazole was associated with a smaller increase (~1.43-fold) [9].
However, in the ADMIRAL study, the use of posaconazole, itraconazole, and voriconazole was not allowed, and thus the experience of administering these drugs together with Gilteritinib is currently limited [10].
It can be seen from the data sheet that dose reduction of Gilteritinib in case of prophylaxis with azoles is not recommended, but close monitoring of Gilteritinib-related toxicity is recommended [11].
At present, experiences analyzing the incidence of invasive fungal infections in patients on Gilteritinib (25%) [12], whether prophylactically treated or not, are rare.
In light of this evidence, it also becomes essential to evaluate the incidence of side effects related to the use of antibiotic/antifungal/antiviral drugs in the prophylaxis and treatment of infections in the setting of relapsed/refractory patients undergoing continuous therapy such as Gilteritinib.

Study design

The study is observational, retrospective-prospective, multicenter "real-life" study involving 26 centers belonging to the SEIFEM group. Regarding the retrospective part, clinical data will be collected on all patients with LMA FLT3+ (ITD or TKD mutation) treated with Gilteritinib from when the drug was approved and marketed in Italy (April 2, 2020) until April 30, 2022. Enrollment in the prospective cohort will have an estimated duration of 24 months from the time of study approval. Patients enrolled in the last month will be followed for six months from the date of enrollment to check for the occurrence of any infections. For each case of a patient receiving salvage monotherapy with Gilteritinib, a control patient with LMA R/R FLT3+ on salvage chemotherapy should also be included.

Study Duration.
Relative to the prospective part, the study will have a total duration of 24 months from the first patient enrolled and six months of observation from the last patient enrolled.

Population

Inclusion criteria:
- All patients with FLT3+ relapsed/refractory AML to any line of therapy treated with Gilteritinib
- Patients ≥18 years of age
- Signature of appropriate informed consent

Exclusion criteria:
- Patients < 18 years old

Study Objectives.
The purpose of the present retrospective/prospective study is to evaluate the "real life" incidence of infectious complications in patients with relapsed/refractory FLT3+ AML treated with Gilteritinib.
Primary objective
To assess "real-life" in patients with relapsed/refractory FLT3+ LMA treated with Gilteritinib the absolute infectious risk and compare it with relapsed/refractory patients receiving chemotherapy.
Secondary objectives.

- To assess the site, incidence and outcome of bacterial/fungal/viral infections in this patient setting
- To assess the need for hospitalization and the duration of hospitalization
- To analyze the different antifungal prophylaxis policies in different Hematology Centers and correlate them with the incidence of infection
- To analyze the incidence of side effects related to the use, in combination with Gilteritinib, of antifungal/antibacterial/antiviral drugs (in prophylaxis/therapy).

Methods

The proposed study is retrospective-prospective, multicenter, observational.
Data will be retrospectively collected from all cases observed from April 2, 2020 until April 30, 2022 about the infectious event and related treatment information (database attached).
In the prospective cohort, enrollment will have an estimated duration of 24 months from the time of study approval. Patients enrolled in the last month will be followed for six months thereafter to check for the occurrence of any infections.
Data from patients with gilteritinib monotherapy and data from patients for whom the clinician's choice is the use of chemotherapy (consisting, for example, of the following regimens: FLA-IDA, MICE, MEC, intermediate/high-dose cytarabine) will have to be analyzed to assess the infectious risk associated with gilteritinib monotherapy.
It is reiterated that since this is an observational study, the choice of therapy is at the discretion of the treating hematologist and independent of enrollment in this study.
Informed consent will be sought from all patients still alive at the time of initiation of data collection and from patients whose data will be collected prospectively. However, it should be noted that since this is a study that mainly considers patients with relapsing hemopathies that could be complicated by life-threatening infections, the rate of obtainable consents may be reduced due to the mortality of these hemopathies.
The incidence of infection will be related to the following variables:
- Age
- Sex
- Comorbidities
- Type of antimicrobial prophylaxis performed
- Type of FLT3 mutation (ITD vs TKD)
- Type of response to treatment
- Hospitalization and duration

Any side effects related to the combination of Gilteritinib with antimicrobial drugs used in prophylaxis/therapy by different centers will also be evaluated.
The study will not affect normal care practice in any way, as there is no blood sampling for patients.
Each patient and each control will be assigned an identification code that will allow the omission of any reference that would allow patient recognition.
Clinical information will pertain to the coordinating center and will be collected within a database.
Based on the following considerations:
- it is assumed that the reference population, or target population from which the sample is drawn (78 patients), is Gaussian distributed with unknown variance;
- the null hypothesis (superposibility of the two populations: sample and target) is rejected if the sample mean differs from the mean value of the reference population by an amount, in absolute value, equal to or greater than 36.7 percent of the standard deviation;

- we adopt, for testing the hypotheses (null and alternative), the two-tailed Gauss z-test with $\alpha = 0.05$ (error of the first kind) and $\beta = 0.10$ (error of the second kind), which implies, as is well known, a test power of 90%;
at least 78 patients are expected to be enrolled.
The analysis will be aimed at evaluating the distribution of infectious events (viral/bacterial/fungal) and identifying parameters that significantly influence the outcome of infectious complication.
With regard to descriptive statistical analyses, central tendency, variability, symmetry and kurtosis will be calculated, all accompanied by appropriate graphical representations; with regard to inferential analyses, in addition to multivariate binary logistic regression, parametric and nonparametric hypothesis testing will be carried out, respectively, for quantitative variables with parametric tests such as: Student's t-test, Fisher's F-test, etc. and for categorical variables by nonparametric tests such as: chi-square, Mann Witney's U, Fisher's exact test, etc. Only results with p-values ≤ 0.05 will be considered statistically significant.

The study does not involve any expenses related to data collection or additional examinations.
Italian Hematology Centers belonging to the SEIFEM Group, which includes both university and hospital facilities, will participate in the study (Appendix 1: list of participating centers).
Data collection and analysis and report preparation will be the responsibility of the scientific board.

Dissemination of results
Publication of results in leading international scientific journals dealing with topics related to hematology and infectious diseases. Also, presentation of results at major national and international hematology congresses, (American Society of Hematology, European Hematology Association, Italian Society of Hematology)