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Real-Life Study on Gilteritinib-Related Infections (GilteRInf): An Italian SEIFEM Study

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To the Editor,

Patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) represent an exceedingly fragile population. This vulnerability stems from a combination of factors: prolonged cytopenia secondary to previous intensive chemotherapy and the inherent immunosuppressive nature of the underlying malignancy [1]. In this context, infectious episodes (IEs) remain a primary cause of morbidity, often delaying the delivery of subsequent treatments. The therapeutic landscape for R/R FLT3+ AML has been significantly transformed by the introduction of gilteritinib, an oral FLT3 inhibitor, which has demonstrated superior efficacy compared to salvage intensive chemotherapy in patients harboring such mutation [2]. However, most available data regarding IEs during gilteritinib therapy originate from clinical trials, which predominantly report data through the lens of broad categories such as febrile neutropenia or pneumonia. Consequently, there is a scarcity of real-world evidence detailing the specific localization, etiology, timing, and outcomes of IEs in unselected patient populations. Based on these considerations, we conducted a multicenter, cross-sectional, real-world observational study to provide a comprehensive assessment of IEs in 123 consecutive adults with R/R FLT3-mutated AML treated with gilteritinib monotherapy across 18 GIMEMA-SEIFEM centers (April 2020–January 2025). IEs, including fever of unknown origin (FUO) and microbiologically documented infections, were graded per CTCAE v5.0. [3]. Invasive fungal diseases (IFDs) were categorized according to EORTC criteria [4]. Baseline variables were collected via standardized electronic CRFs. Statistical analyses

Maria Ilaria Del Principe and Livio Pagano contributed equally to this study.

utilized Shapiro–Wilk for normality, Mann–Whitney U or *t*-tests for continuous variables, and Chi-squared or Fisher's exact tests for categorical data. Survival outcomes were estimated using the Kaplan–Meier method with log-rank tests. Univariate and multivariate logistic regression models identified predictors for IE onset. Analysis was performed using SPSS v30.0. The study was approved by the central Ethics Committee (n°R.S.82.22) and registered on ClinicalTrials.gov (NCT05791890).

The demographic and disease characteristics of the group are described in Table S1. We recorded 82 FUO episodes and 113 microbiologically documented IEs, of which $n=68$ (60%) Grade (G) ≥ 3. Overall, 49% ($n=60$) of patients had ≥ 1 FUO, 60% ($n=74$) ≥ 1 IE, 42% ($n=52$) at least one G ≥ 3 IE. In Table 1, the detailed characteristics and outcomes of the IEs are depicted.

While no primary antibacterial prophylaxis was administered, 35 cases (28%) received antifungal prophylaxis with posaconazole. At the onset of the IEs, the median absolute neutrophil count was 300/mcl (range 0–23 760/mcL). Stratifying the cohort for allogeneic-hematopoietic stem cell transplantation (allo-HSCT) status (yes/no 36/87), the number of IEs per patient and infection severity was similar between groups (respectively $p=0.972$, $p=0.645$), however lung infections were more frequent among patients with prior allo-HSCT (60% vs. 37%) ($p=0.059$) and IFDs predominated post-transplant ($p=0.007$) (Table S2). The cumulative incidence analysis of IEs demonstrated that the majority (60%) occurred within the first 90 days from treatment initiation, while 80% had occurred by 180 days. Non responders experienced IEs earlier than responders ($p=0.004$) (Figure S1). Overall, infection-related mortality was 18% ($n=20$), comprising 5 at 30 days and 11 at 60 days. Restricting analysis to gilteritinib responders, fatal IEs accounted for 5% ($n=6$) of deaths. Among the G5 events, 8 were bacterial sepsis (42%), and 12 were pneumonia (58%). Out of the 12 pneumonia cases 3 (25%) were bacterial, 2 (16.7%) were caused by SARS-CoV-2, 1 (8.3%) was caused by *Pneumocystis jirovecii*, and 6 (50%) were IFDs (4 of which proven/probable). Overall, 11 (55%) G5 IEs occurred in refractory patients. In survival analysis, the presence of ≥ 1 IE was significantly associated with a shorter OS ($p=0.016$), an association that was maintained when restricting the analysis to gilteritinib responders ($p=0.012$) (Figure 1A–C). Logistic regression analysis identified no statistically significant predictors of overall infection risk ($p=$ ns). However, among G5 IEs, refractory disease was associated with > 5-fold increased odds (OR: 5.26; 95% CI: 1.71–16.24; $p=0.004$).

Recently, Ceprano et al. [5] published a multicenter real-world Italian study on 205 patients treated with gilteritinib from 2018 to 2024. This study however, focused primarily on clinical outcomes while not addressing IEs or infection-related mortality in detail. Within our cohort, the infectious burden was substantial: 60% ≥ 1 IE, 42% at least one G ≥ 3 IE. FUO during neutropenia occurred in nearly half of the patients (49%), a rate comparable to that reported in the phase 1–2 trial of gilteritinib [6] (39.4%) and in the ADMIRAL study (46.7%). Conversely, pneumonia incidence in our cohort (30%) was markedly higher than in the phase 1–2 study (13.6%) and ADMIRAL trial (17.5%). Our sepsis rate (26%) substantially exceeded that observed in the phase 1–2 trial (14.4%), but this outcome was not specifically reported in ADMIRAL. These discrepancies between trial results and our findings stem directly from the contrast between a highly selected clinical trial population and an unselected cohort; in fact, although the median age was comparable between ADMIRAL and our

TABLE 1 | IEs characteristics.

Infection localizations (%)	*N* = 113
Lungs	46 (41)
UTI	11 (10)
Sepsis	40 (35)
Other	16 (14)
Infection types (%)	
– Bacterial	77 (68)
Multisensitive gram-negative bacteria	34 (30)
ESBL gram-negative bacteria	7 (6.1)
CRE bacteria	6 (5.3)
S.aureus	2 (1.7)
Gram-positive bacteria—CVC (PICC) related sepsis	19 (16.8) – 4 (3.5)
VRE bacteria	1 (0.9)
Clostridium difficile	4 (3.5)
– Viral	4 (3.5)
HSV	1 (0.9)
Influenza A	3 (2.6)
– SARS-CoV2	12 (10.5)
– Fungal	17 (15)
Proven/probable	8 (47)
Possible	9 (53)
– *Pneumocystis jirovecii*	3 (3)
Grading (%)	
1–2	45 (40)
3–4	48 (42)
5	20 (18)
Need hospitalization or prolonged hospitalization (%)	76 (67)
Outcomes (%)	
Resolved in 30 days	55 (48.6)
Resolved in 60 days	27 (23.8)
Resolved in 90 days	6 (5.4)
Deaths with infection within 90	20 (17.7)
Deaths for other reasons without infections within 90 days	5 (4.5)

Abbreviations: CRE: Carbapenem-resistant Enterobacterales; ESBL: Extended spectrum beta lactamase; N: Number; SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus 2; UTI: Urinary tract infections; VRE: Vancomycin-resistant enterococci.

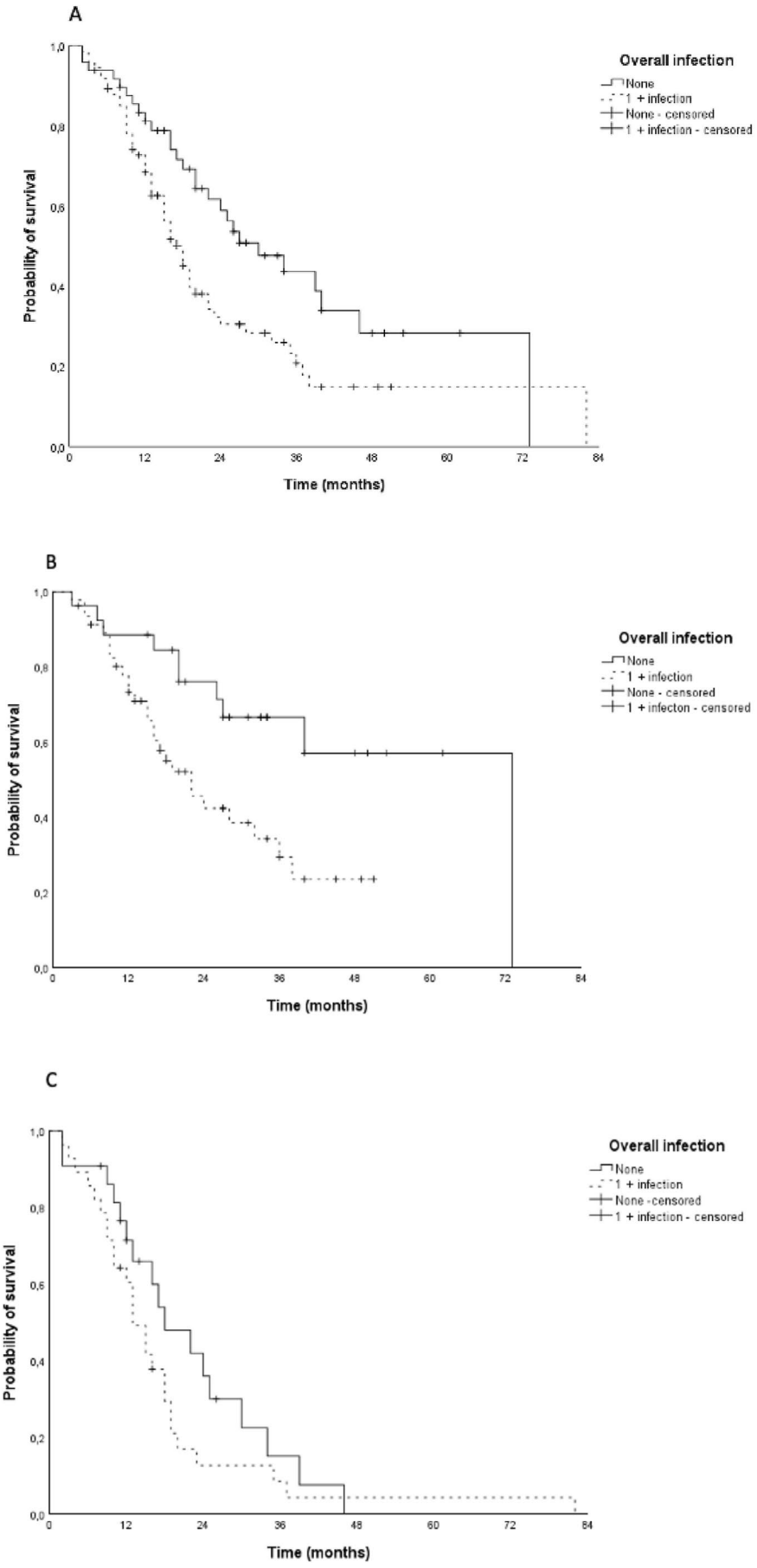

FIGURE 1 | Overall survival related to infectious events. (A) Overall. (B) Responders to gilteritinib. (C) Non-responders.

study (62 vs. 63 years), trial eligibility required an ECOG < 3, whereas our cohort also included patients with ECOG 3–4. Moreover, ADMIRAL enrolled patients who relapsed after 1 chemotherapy cycle or were refractory after 2, whereas 8 of ours had > 2 prior cycles. In a pharmacovigilance study [7], based on spontaneously reported adverse events with FLT3 inhibitors—including gilteritinib, but without a defined patient cohort—pneumonia and fever were the events most frequently associated with fatal outcomes. However, the analysis did not specify the underlying etiology or classification of the pneumonias, nor did it report the total number of individuals represented by these safety reports. In our study cumulative incidence analysis documented that most IEs occurred within the first 90 days of gilteritinib therapy, a critical period during which patients exhibit maximal vulnerability due to profound immunosuppression related to incomplete blast clearance. Gilteritinib response stratification showed clear differences: non-responders experienced substantially more early IEs than responders, highlighting disease control as a key determinant of infectious risk. Moreover, the data exhibit a statistically significant correlation between prolonged neutropenia and the occurrence of IEs: patients who experienced ≥ 1 IEs had a longer median duration of neutropenia compared to those who did not ($p = < 0.01$). Furthermore, the profound bone marrow suppression is highlighted by the very low median neutrophil count at infection onset (300/mcl). In our cohort, 67% of IEs required either prolongation of an ongoing hospital stay or admission from home, underscoring the severity of these events and the associated costs to the national health system. Analysis of infection-related deaths revealed 20 G5 IEs overall. However, most occurred in patients who were refractory to gilteritinib and therefore had active disease, making it unlikely that infection was the primary cause of death. When the analysis was restricted to patients in CR, infection-attributable mortality was 5%. Among risk factors for developing a G5 IE, only refractory disease showed a significant association. When analyzing the survival curves, the occurrence of ≥ 1 IE was clearly associated with shorter OS in our cohort (18 vs. 30 months), indicating that infections are not just frequent complications but clinically meaningful events that can alter the disease trajectory. Notably, among gilteritinib non-responders, median OS did not differ significantly between patients with or without IEs, whereas among responders, IEs were associated with a dramatic reduction in OS. Clearly, infectious burden acts as a negative prognostic marker, likely reflecting periods of treatment interruptions, and delays of gilteritinib and long antibiotic therapies, all of which may compromise long-term outcomes. Consistent with this interpretation, in our series, 14 patients permanently discontinued gilteritinib because of an infection. In contrast, in the ADMIRAL trial the number of IEs leading to permanent discontinuation of gilteritinib was not explicitly reported, instead, individual IEs were listed separately as reasons for treatment discontinuation (pneumonia 1.2%, febrile neutropenia 0.4%, septic shock 0.8%, etc.). In our study, among patients previously exposed to allo-HSCT, the transplant procedure itself did not emerge as a risk factor for developing IE. In fact, the overall rate of IE was comparable between patients with and without prior allo-HSCT ($p = 0.97$), and previous transplantation was not associated with an increased odds of experiencing at least one IE ($p = 0.61$), probably because allo-HSCT is performed upfront in high-risk patients—resulting in lower cumulative prior therapy exposure—whereas several of our not-transplanted patients had received multiple prior treatment. However, the infection pattern differed by transplant status: among previously transplanted patients, IEs tended to involve the lungs more frequently, with pneumonia accounting for 60% of IE ($p = 0.059$). This predominance of pulmonary infections is consistent with the post-ADMIRAL study [8], where G ≥ 3 pneumonia occurred in 25% of patients resuming gilteritinib after allo-HSCT, while in our transplanted cohort G ≥ 3 pneumonia was observed in a 36%. Importantly, the post-ADMIRAL report did not characterize the etiology of pneumonia, whereas in our study the infectious agents were systematically documented, revealing a clear shift toward fungal pathogens in the post-transplant setting. Overall, in our cohort, IFDs occurred in a 13.8% of cases, of which 82.4% experienced a G ≥ 3 IFD. Excluding possible cases, the rate of probable/proven IFD was 6.5%. Literature data on IFDs incidence during gilteritinib therapy remain scarce: in the phase 1–2 trial G ≥ 3 fungal pneumonia occurred in 4% of patients (categorization as possible/probable/proven unspecified), while IFDs were not specifically reported in the registration trial. Given the severe disease-related myelosuppression and the high incidence of G ≥ 3 IEs in our study, including a significant rate of fungal complications, a prompt therapeutic approach is highly recommended in case of probable fungal IE, in fact in this high-risk hematological setting identifying patients at high risk and implementing timely, optimized antifungal strategies remains crucial to improve clinical outcomes [9, 10].

While our findings picture a substantial infectious burden during gilteritinib therapy, these results must be interpreted with caution, acknowledging the inherent complexity of a salvage setting where patient's individual response to the drug and prior infectious history represents potential confounding factors.

Author Contributions

Conceptualization: E.B., M.I.D.P., and L.P. Formal analysis: I.T. Investigation: M.T., F.L., S.P., C.P., G.M., F.F., L.F., M.Q., N.F., C.F., M.A., A.L.P., D.F., CM. B., C.B., N. DR., M.P., MG.C., D.A., and F.M. Writing – original draft preparation: E.B. Writing – review and editing: M.T., F.L., S.P., C.P., G.M., F.F., L.F., M.Q., N.F., C.F., M.A., A.L.P., D.F., C.M.B., C.B., N. DR., M.P., M.G.C., D.A., A.V., A.B., and F.M.: Supervision: M.I.D.P., L.P.

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Ethics Statement

Procedures complied with the Declaration of Helsinki. The study obtained central Ethics Committee approval from the coordinating center (n° R.S.82.22) plus site-specific approvals as needed. With respect to privacy, all personal information was treated in a confidential manner, and all clinical data were anonymized.

Consent

Written informed consent was obtained from all subjects involved in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All relevant data are included in this article. For additional data inquiries, a request can be directed to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Clinical and demographic characteristics. *n*: number; IE: infectious event; IQT: interquartile interval; CR: complete remission; PR: partial remission; allo-HSCT: allogeneic hematopoietic stem cell transplant; ECOG: eastern cooperative oncology group; TKI: tyrosine kinase inhibitor; SD: stable disease; OS: overall survival. * allo-HSCT or lost to follow up. **Table S2:** Stratification based on previous allo-HSCT. Allo-HSCT: allogeneic Hematopoietic Stem Cell Transplantation; IE: infectious events; UTI: urinary tract infection; SARS-CoV2: severe acute respiratory syndrome Coronavirus 2. **Figure S1:** (A) overall cumulative incidence of IEs. (B) cumulative incidence of IEs stratified for response to gilteritinib.