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Successful remission induction therapy with gilteritinib in a patient with *de novo FLT3*-mutated acute myeloid leukaemia and severe COVID-19

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To the editor,

The optimal treatment for patients with newly diagnosed acute myeloid leukaemia (AML) who are infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)/COVID-19 is unknown.[1] We report the case of a previously fit 27-year-old male who presented with a 3-day history of fever (>39^{o}C), swollen, erythematous elbows and no respiratory symptoms. His white blood count (WBC) was 187×10^{9}/L and bone marrow (Figure 1A & 1C) examination revealed normal karyotype AML with a fms related receptor tyrosine kinase 3 (*FLT3*) internal tandem duplication (ITD), wild-type *NPM1* and no additional mutations on a next-generation sequencing panel.

Hyperleukocytosis was immediately treated with hydroxycarbamide, dexamethasone, rasburicase (for tumour lysis syndrome prophylaxis), and 3 doses of 100mg/m^{2} cytarabine over the first 48 hours. He received antibiotics to treat febrile neutropenia and cellulitis and although he denied any respiratory symptoms, a combined nasal and pharyngeal swab for SARS-CoV-2 RNA was positive. Ultrasound doppler revealed a lower-limb deep vein thrombosis, bilateral upper-arm superficial thrombophlebitis and coagulation markers were indicative of disseminated intravascular coagulation (DIC; Figure 1B). Given his active SARS-CoV-2 infection and the presence of a *FLT3*-ITD mutation, he was treated with single-agent gilteritinib, an oral *FLT3* inhibitor,[2] from day 3. Gilteritinib shows superior efficacy to salvage chemotherapy in relapsed/refractory *FLT3*-mutated AML,[3] with low rates of infection and early mortality, although it is not currently licensed for use in *de novo* AML.

On day 6, he became hypoxic, with hyperpyrexia, rising C-reactive protein (CRP; Figure 1B), and a high-resolution CT scan of the chest (HRCT; Figure 1D) showed changes typical for COVID-19. He was transferred to the intensive care unit on day 7 for continuous positive airway pressure (CPAP) support, but deteriorated further on day 13, requiring emergency intubation due to adult respiratory distress syndrome (ARDS). Dexamethasone was briefly restarted on day 14 to treat early differentiation syndrome.[2] He was extubated to CPAP on day 20, however, he experienced a febrile episode associated with seizures on day 22 due to *Escherichia coli* bacteraemia, which precipitated

re-intubation, vasopressor support and further antibiotics. Gilteritinib was temporarily discontinued for 7 days from day 25 (Figure 1A) due to biochemical features of septic shock-related cardiomyopathy.

During the admission, the patient experienced only 5 days of severe neutropenia ($<0.5\times10^9$/L) and 17 days of thrombocytopenia ($<50\times10^9$/L). Post-induction bone marrow examination showed morphological (Figure 1C) complete remission and a significant reduction in *FLT3*-ITD allele ratio from 0.66 at diagnosis to 0.07. He received a tracheostomy without incident on day 33. A repeat HRCT on day 39 (Figure 1D) showed extensive changes associated with severe COVID-19. He was decannulated on day 45 and transferred back to the ward for intensive rehabilitation. SARS-CoV-2 RNA remained detectable on weekly nasopharyngeal swabs until day 60 when it became undetectable. At the time of writing, he continues on gilteritinib, with a plan to proceed to allogeneic stem cell transplantation when he is physically fit.

Though the effects of SARS-CoV-2 infection on patients with AML are largely unknown,[1] early evidence suggests that patients with active haematological malignancies and COVID-19 have more severe disease and a higher case fatality rate.[4-5] Provisional guidance[1,6] recommends delaying AML induction chemotherapy in patients with concurrent COVID-19, an option not possible in this case. Induction mortality rates with intensive chemotherapy in those with hyperleukocytosis can approach 30% and such chemotherapy is associated with prolonged pancytopenia (often >3 weeks) and high rates of severe infections.[7] We conclude that single-agent gilteritinib can be safely administered and induce remission in patients presenting with *de novo FLT*3-ITD positive AML. Although further studies are required in this setting, gilteritinib can be considered as a treatment option for patients with *FLT3*-mutated AML and severe COVID-19, where a prolonged period of chemotherapy-induced pancytopenia could adversely affect outcomes.

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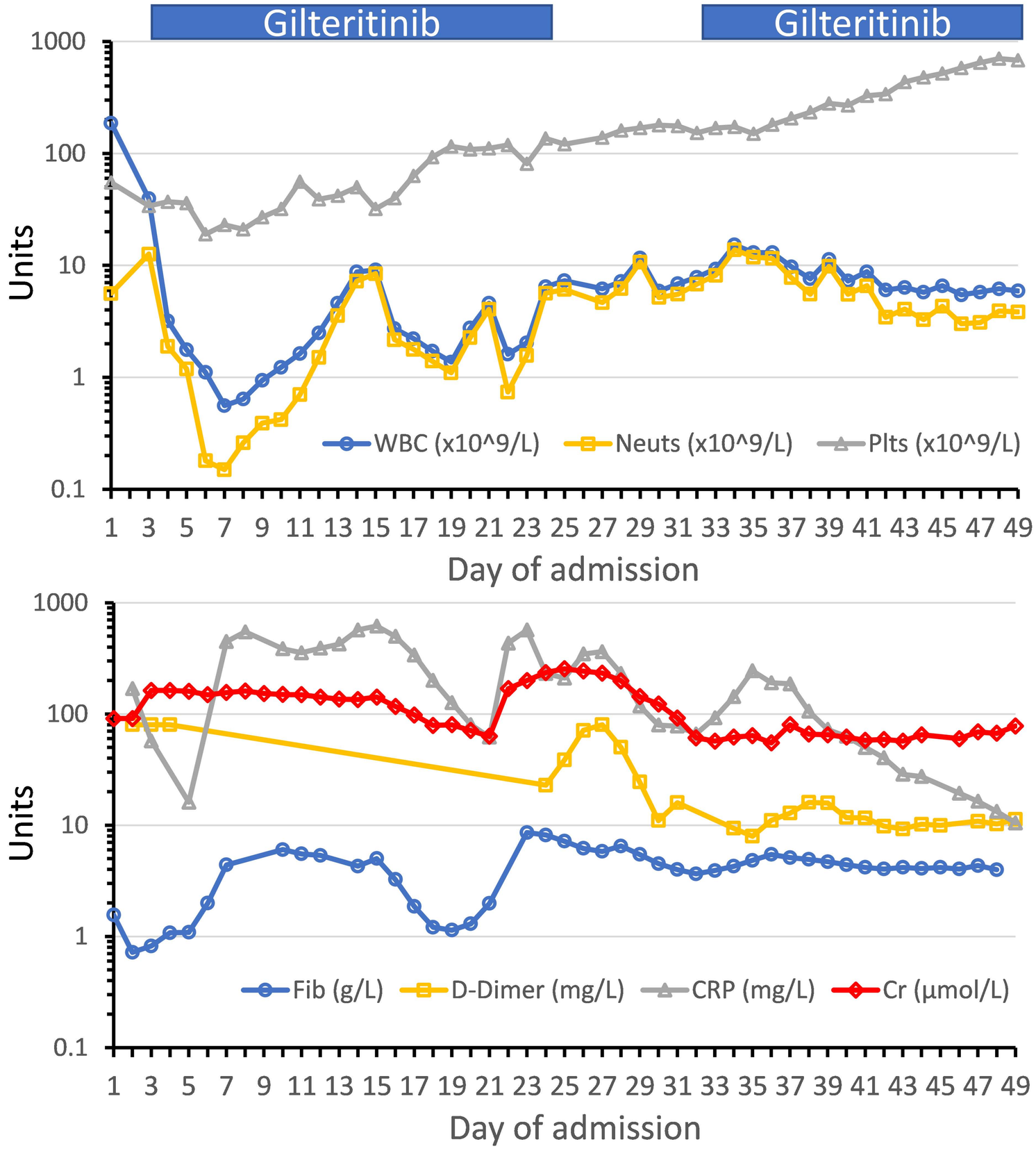
Conflicts of Interest

AW: personal fees from Novartis, MRM: advisory boards for Janssen, EP: advisory boards for Novartis, Celegene and Takeda, AK: personal fees from Astellas, outside the submitted work. ETB, The other authors have no conflicts of interest to declare.

Figure 1

Complete blood count parameters are shown in Panel A; white blood count (WBC, reference range 3-10×10^9/L), neutrophils (2-7.5× 0^9/L) and platelets (150-400×10^9/L). Gilteritinib administration (120mg once daily), starting from day 3 onwards, is indicated by blue bars. The patient presented with high d-dimers >80mg/L (range<0.5mg/L; Panel B) and hypofibrinogenemia (range 1.5-4g/L), followed by a hyperfibrinogenemic stage during which C-reactive protein (CRP; range <5mg/L, Panel B) peaked. Mild tumour lysis syndrome developed with a near doubling of baseline creatinine (range 66-112 µmol/L; Panel B). Morphological analysis of the bone marrow smear at diagnosis (Panel C, top pane) showed heavy infiltration by myelomonocytic blasts, which were positive for CD34, CD117, HLA-DR, CD33, CD15, CD38, cytoplasmic myeloperoxidase and weakly positive for CD7 by flow cytometry (not shown). The post-induction bone marrow smear showed morphological (Panel C, bottom pane) and flow cytometric complete remission. The initial high-resolution CT (HRCT) scan on day 6 (Panel D, top pane) displays patchy infiltrates with extensive patchy areas of ground glass opacification and 'crazy paving' pattern, typical of severe COVID-19. Repeat HRCT at day 39 (bottom pane) showed widespread ground glass opacification, as well as areas of consolidation and a progressive left sided pleural effusion.

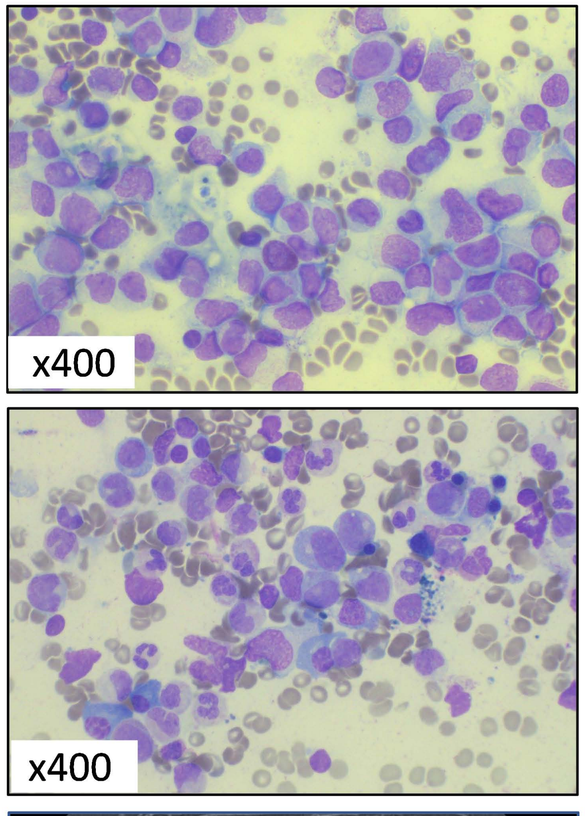
A


Gilteritinib
Gilteritinib
1000
100
10
1
0.1
Units
WBC (x10^9/L)
Neuts (x10^9/L)
Plts (x10^9/L)
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49
Day of admission

B

1000
100
10
1
0.1
Units
Fib (g/L)
D-Dimer (mg/L)
CRP (mg/L)
Cr (µmol/L)
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49
Day of admission

C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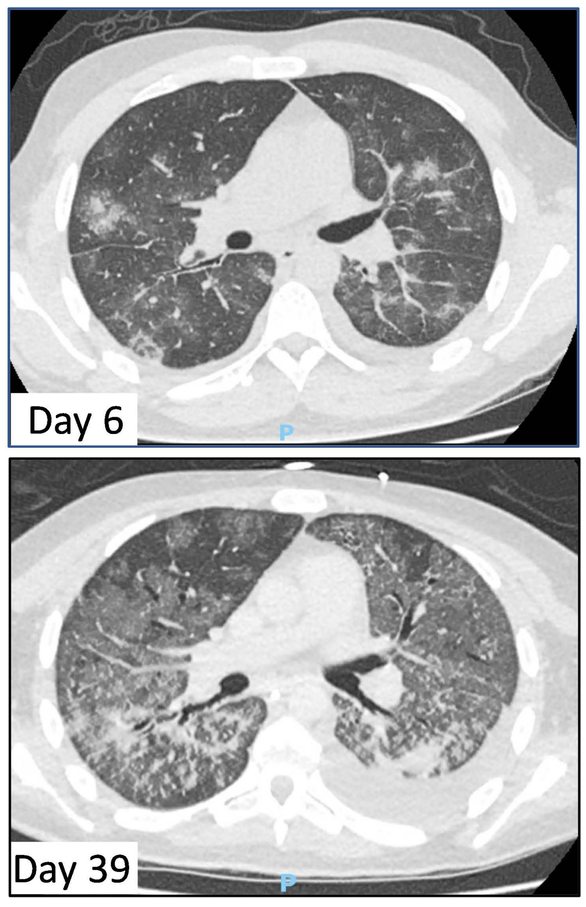
D


Day 6
Day 39