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COMMENTARY

Early treatment for COVID-19 in patients with haematological malignancies: Much more than a recommendation!

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Patients with haematological malignancies (HM) are especially vulnerable given the increased risk of SARS-CoV-2 infection, morbidity, and mortality. In high-risk non-hospitalized patients, nirmatrelvir (NR) can significantly reduce the rate of hospitalization or death when administered within 3–5 days after the onset of symptoms. A new study from Italy supports the effective role of NR in preventing pulmonary complications and death in high-risk HM patients.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in December 2019 had important consequences on health systems across the world. Patients with haematological malignancies (HM) were especially vulnerable given the increased risk of SARS-CoV-2 infection, morbidity, and mortality.[1] To prevent global disruption of HM care and manage COVID-19 in the pandemic, the EHA (European Hematology Association) and the ESMO (European Society for Medical Oncology) rapidly launched an interdisciplinary expert consensus.[2]

Despite being associated with poor antibody response in HM,[3] COVID-19 vaccination remains the most important line of defence against SARs-CoV-2 infection, reducing COVID-19 complications (i.e. severe disease, hospitalization and death). Besides immune impairment related to HM, JAK inhibitors and B-cell-depleting therapies affect the immune response to COVID-19 and vaccination during and for up to 12 months after the end of treatment.[4] However, vaccination has been proven to sustain long-term T-cell-mediated immunity, also in patients with poor antibody response or receiving B-cell-depleting therapies.[5,6] Overall, according to the EPICOVIDEHA survey, mortality for COVID-19 dramatically changed post-vaccination (8%) compared to prevaccination time (31%).[7] Since May 2020, monoclonal antibodies (mAbs) functioning as passive immunity targeting the spike protein of SARS-CoV-2 (regdanvimab, sotrovimab, casirivimab/imdevimab, tixagevimab/cilgavimab and bamlanivimab, either as monotherapy or in combination with etesevimab) proved to prevent COVID-19 in patients at high risk of severe disease as either pre-exposure or post-exposure prophylaxis. Some were authorized, with either full or conditional approval specifically for early outpatient treatment of high-risk COVID-19 subjects. The widespread use of mAbs was limited during the pandemic by availability, cost, and logistics and, more recently, by the emergence of escape mutants. Tixagevimab and cilgavimab (Evusheld) entered clinical practice for pre-exposure prophylaxis in HM patients on the basis of a phase 3 study[8] until January 2023, when new non-susceptible Omicron subvariants (XBB.1.5, BQ.1.1) were projected to be more than 90% of infections in the United States. A 32%-rate of immunocompromised patients receiving sotrovimab developed spike protein mutations that substantially reduced susceptibility to sotrovimab in a neutralization assay.[9]

As a general statement on HM, special consideration should be paid for those patients, who are unvaccinated/partially vaccinated/last shot received more than 6 months earlier, or with an expected low serum conversion (B-cell–depleting therapy, JAK inhibitors and hypogammaglobulinemia), or on active treatment, or within 2 years of stem-cell transplant or CAR-T therapy. Patients with mild-to-moderate COVID-19 and HM in these clinical situations should be considered for early, outpatient, antiviral

treatments (Figure 1). Conversely, early recognition of severe/critical COVID-19 requires a fast track to hospitalization.

Among antivirals, ritonavir-boosted nirmatrelvir (NR) has proven efficacy to reduce the rate of hospitalization or death by 89% when administered within 3–5 days after the onset of symptoms, in high-risk non-hospitalized patients in the EPIC-HR trial.[10] Nirmatrelvir blocks the activity of SARS-CoV-2-3CL^{pro} protease, an enzyme needed for viral replication. As 3CL^{pro}, the substrate-binding site, is highly conserved among all coronaviruses and shares no homology with human proteases, a SARS-CoV-2-3CLpro antagonist can be highly specific to SARS-CoV-2 and less affected by virus mutations compared to antivirals binding to other sites. Given the inactivation of CYP3A4 by ritonavir, a careful analysis of drug–drug interaction is compulsory before starting NR. Notably, patients with severe renal or hepatic dysfunction are not eligible for NR. Molnupiravir (MOL) is a nucleoside analogue prodrug of N-hydroxycytidine. Phosphorylated N-hydroxycytidine is incorporated into the viral RNA, leading to an accumulation of deleterious errors in the viral genome thereby halting viral replication. Immunocompromised subjects ($n = 53$) enrolled in the phase 3 MOVe-OUT trial who received MOL had a lower incidence of all-cause hospitalization or death (8.3% vs. 22.6%).[11] Recently, the European Agency of Medicines (EMA) did not recommend marketing authorization for MOL as the clinical benefit in high-risk patients not receiving supplemental oxygen could not be demonstrated.

In this issue, Minoia et al.[12] studied prospectively a cohort of 82 HM patients (63 with lymphoproliferative neoplasms, 14 with myeloid neoplasms and 5 with multiple myeloma) treated with NR or MOL for COVID-19 in the outpatient setting. All patients had been treated for their HM within 12 months. COVID-19-related lung failure was 23.1% and COVID-19-related deaths at 28 days were 6.1%. Although there was no control arm, the data provide some further support for the use of antivirals for HM patients in the early phase of COVID-19 prior to clinical progression.

Additionally, remdesivir (RDV), a phosphoramidite prodrug of a monophosphate nucleoside, acts as a viral RNA-dependent RNA polymerase (RdRp) inhibitor, targeting the viral genome replication process. Once metabolized into its pharmacologic active analogue adenosine triphosphate (GS-443902), RDV competes with ATP for integration by the RdRp complex into the nascent RNA strand and, upon subsequent incorporation of a few more nucleotides, results in the termination of RNA synthesis, limiting viral replication. In non-hospitalized patients with COVID-19 at high risk for disease progression, a 3-day course of intravenous RDV resulted in an 87% relative reduction of hospitalization or death compared with a placebo.[13] Hence, RDV represents an alternative to NR in eligible patients presenting within 7 days of symptom onset. Notably, like NR, RDV is not recommended in patients with severe renal impairment and the 3-day IV dosing regimen poses logistical challenges, particularly for outpatient administration.

Figure 1 provides a practical COVID-19 management tool for doctors and patients, based on the current availability of medications. It is important to reiterate that fragile HM patients should maintain moderate social distancing and hand

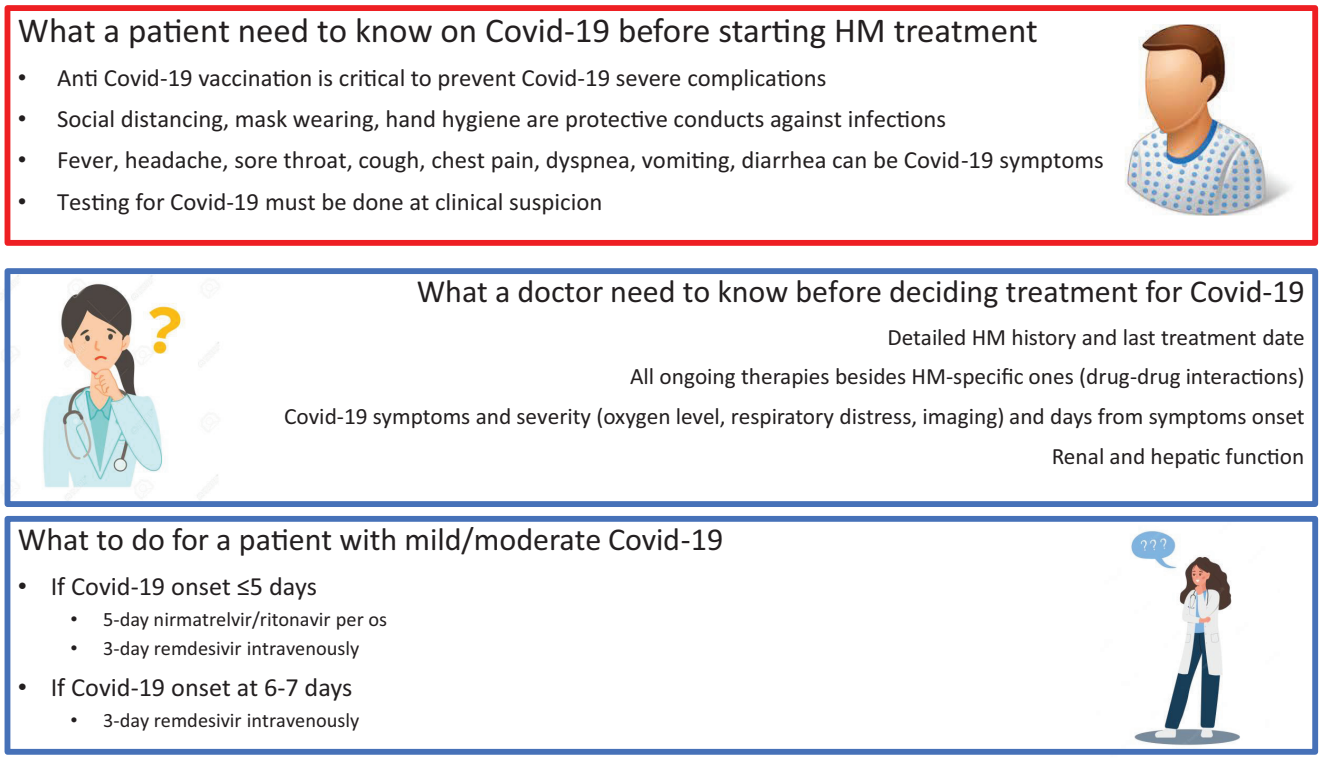

FIGURE 1 Managing COVID-19 in haematological malignancies.

hygiene, with mask-wearing in high-risk situations, and that all household members should be vaccinated.

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