AML AND COVID-19 PANDEMIC

Induction and consolidation therapy in acute myeloid leukemia (AML) patients results in a high risk of infectious complications. In particular, severe and prolonged neutropenia with neutrophil counts below 500/µl or even 100/µl leads to an increased risk of febrile complications, due in most cases to bacterial or fungal infections (1). Respiratory virus infections can also occur in AML patients, particularly during seasonal outbreaks, and their recognition has been facilitated by the recent widespread use of molecular microbiologic testing. Their incidence varies widely between 1% and 50% in different series and for different respiratory viruses. Progression from an upper respiratory tract infection (URTI) to a lower respiratory tract infection (LRTI), with frequent bacterial and fungal co-infections, is associated with an increased likelihood of fatal outcome, reported in 5-54% of cases. The respiratory viruses most frequently associated with an adverse prognosis are influenza, parainfluenza, respiratory syncytial virus, adenovirus and human metapneumovirus (2). Although human Coronavirus (HCoV) has not been considered among the most aggressive respiratory viruses, there have also been well-documented cases of severe and even fatal LRTI in HCoV+ hematologic patients (3,4). While these complications would suggest the use of antiviral prophylaxis, the benefit of such an approach remains unproven; it is therefore neither recommended nor utilized in most institutions and viral surveillance seems to be more widely utilized in acute lymphoblastic leukemia than in AML (5,6). COVID-19 is affecting 188 territories around the world and causes illnesses ranging from the common cold to more severe diseases mimicking the Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). The clinical characteristics of the COVID-19 epidemic are being actively studied (6). At difference with the most common respiratory viruses, it is frequently complicated by bilateral interstitial alveolar pneumonia and respiratory insufficiency whose pathogenesis is sustained by a marked cytokine release syndrome. A worldwide rise in the number of daily confirmed cases has led the World Health Organization (WHO) to declare its spread as a global pandemic. We would thus expect that an increasing number of patients with different hematologic malignancies including AML will present with concomitant CoV-2 positivity. No results were found by imputing AML and COVID-19 in the NCBI Pub Med. In addition, no specific recommendations have so far been provided by scientific societies and nothing is known also considering the recent Chinese or Italian experience outbreak. Notwithstanding, a number of questions need to be considered, mainly if the number of COVID-19+ subjects will continue to increase in the general population.

Questions and Recommendations

a) Should all newly diagnosed patients with AML be tested?
Testing should be performed in all newly diagnosed AML patients, but also at the start of the next treatment cycle. Serologic testing should be included if possible, in particular in RNA-positive patients.

b) During the follow-up, should the testing for COVID-19 be limited to patients with respiratory symptoms and/or fever, or should they be tested regularly?
Ideally, all patients should be re-tested before each treatment cycle, even if they have no symptoms. However, testing capacity and availability of tests is country dependent. At least patients with symptoms should have an additional test.

c) Which induction therapy should be considered in young adult COVID-19+ AML patients?
In young adult asymptomatic patients, standard induction therapy should be performed. AML induction therapy does not primarly affect the lymphocytic compartment and patients are more prone to bacterial and fungal rather than viral infections.

For symptomatic patients there are no data available with regard to treatment with hypomethylating agents (HMA) / venetoclax (VEN) combination; there is no evidence that HMA/VEN is less toxic than standard induction therapy and patients also experience long phases of aplasia. In addition, this combination is not yet approved by European Medicines Agency; expected approval will be limited to elderly patients.

Furthermore, postponement of treatment for 7-14 days does not worsen the prognosis. A significant number of AML patients does not require immediate treatment. In these patients treatment can be postponed until RNA negativity is reached and standard therapy can be started in a COVID-19 negative environment. If an immediate treatment is needed, standard therapy should be performed in a COVID-19 positive environment.

d) What about older patients? Should COVID-19 positivity be considered a criterion of unfitness to intensive or even to less intensive approaches like VEN/HMA?
There is no sufficient evidence to replace standard intensive treatment by HMA/VEN (see also point c). If otherwise fit and patients are COVID-19 positive but physicians are concerned about intensive treatment due to COVID-19 symptoms, treatment can be postponed by 7-14 days in patients with low proliferating AML; in patients with proliferative AML treatment with hydroxyurea should be considered.

In addition, information on the genetic risk profile will help to guide treatment decisions, in particular with regard for immediate allogeneic transplant/no-transplant in these older patients. For example, patient with adverse-risk AML should achieve RNA-negativity before transplantation.

e) Should high-dose cytarabine-based consolidation therapy be administered to COVID-19+ patients achieving a complete remission or should a dose reduction be considered?
In general, in COVID-19 positive patients in CR, one should consider to postpone consolidation until virus is cleared. With regard to dosage, intermediate-dose cytarabine is recommended to COVID-19 positive but also to COVID-19 negative AML patients. Numerous studies have shown that there is no difference in outcome as compared to

high-dose cytarabine. In this regard, the day 1/2/3 schedule should be preferred versus the 1/3/5 schedule.

f) What kind of isolation should be used to protect COVID-19+ AML patients as well as other patients and health care workers?

Patients should be managed in a COVID-19 unit by experienced hematologists and nurses in collaboration with pneumologists and intensivists; alternatively, a single room with negative pressure in the hematology ward can be considered.

g) Which treatment should be considered for relapsed patients?

If possible, treatment should be postponed until COVID-19 negativity is achieved. Relapse treatment should be performed according to the algorithms of the individual center; treatment strategies for relapse are also country-dependent and have to be taken into account. Relapse treatment strategies include molecularly targeted therapies whenever possible: gilterinitib for *FLT3*+ patients, ivosidenib and enasidenib for patients with *IDH1* and IDH2 mutations (currently not approved by EMA), respectively; one should also consider to include COVID-19 negative patients in clinical trials if eligibility criteria are met.

The same testing/waiting rules mentioned above (point c) for 1st line patients should be applied.

h) Should allogeneic transplants be performed in COVID-19+ patients?

Allogeneic transplantation remains a centrally important curative strategy in adults with high-risk AML and efforts should be made not to delay admission for transplant if possible. However, allogeneic transplant should be deferred in COVID-19 positive patients up to at least one month from a documented COVID-19 negativity. The potential contribution of anti-SARS-CoV-2 antibody detection is presently unclear, but should be performed if possible. Cryopreservation of donor cells prior to the start of conditioning should be performed before proceeding to transplant and must be confirmed before starting the conditioning regimen. This may require administration of an extra cycle of consolidation as guided by both the clinical setting and MRD data. Consider testing for COVID-19 prior to initiation of consolidation (see also point b).

The risk-benefit calculation may be altered for COVID-19 reconvalescent patients. Therefore, when counselling patients about the benefits and risks of allogeneic transplantation, it is important to specifically discuss both, the possible and largely undetermined impact of COVID-19 infection on patients outcomes as well as possible challenges in terms of accessing ICU capacity if this should be required.

i) Should AML patients with respiratory insufficiency due to COVID-19 pneumonia be referred to the ICU?

This has to be very carefully considered and is highly dependent on the risk profile of AML, the current disease status (CR or not, expected duration of neutropenia), co-morbidity, age, patient wish etc.

Many centers have already developed consensus criteria or ICU Scores for all cancer patients. The individual ICU Score should be defined in each patient in advance.

This guideline was originally developed by our Italian colleagues: Felicetto Ferrara, #Robin Foà, °Adriano Venditti and *Giuseppe Rossi

and was used as the basis for discussion and adaptation within the EHA AML SWG

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