ISA

INTERNATIONAL SOCIETY OF AMYLOIDOSIS

International Society of Amyloidosis recommendations on the management of patients with systemic amyloidosis during the COVID-19 pandemic

Introduction

Patients with systemic amyloidosis should be considered at increased risk of complications and mortality in case of SARS-CoV2 infection. This may be particularly relevant for patients with heart involvement, because subjects with SARS-CoV2 infection and preexisting cardiovascular disease have an increased risk of severe clinical manifestations and death, the infection has been associated with cardiovascular complications, and therapies under investigation for COVID-19 may have cardiovascular side effects [1]. In particular, COVID-19 treatment can include hydroxychloroquine ± azithromycin. This combination is associated with the risk of ventricular arrhythmias related to QT prolongation, and if started close cardiological monitoring or at least regular ECG with QTc is required [1]. This is particularly relevant in patients with amyloid cardiac involvement. In addition, patients with renal involvement might be more susceptible to COVID-19, since they have impaired humoral immunity.

Specific for patients with systemic AL amyloidosis are the immunoparesis observed with the disease and the immune suppressive mechanisms of anti-plasma cell directed therapy such as corticosteroids, chemotherapy and proteasome inhibitors. Yet, on the other end, it has been hypothesized, but not proven, that patients receiving immunosuppressors or immunomodulators may have a milder clinical presentation in case of SARS-CoV2 infection [2-4]. This might be relevant also for patients with AA amyloidosis reactive to autoinflammatory diseases receiving biological therapies, and for patients with amyloidosis who are organ transplant recipients. However, recent data suggest that the outcome of solid transplant recipients admitted for symptomatic COVID-19 is poor with a high mortality rate [5, 6]. In patients with ATTRv amyloidosis, there is no evidence that previous liver transplant poses additional risk of complications and mortality in case of SARS-CoV2 infection. In liver transplant recipients, the dose of immunosuppressants is not high. However, they are generally susceptible to viral and bacterial

infections. The same considerations hold true for patients who underwent domino transplantation receiving the liver of a patient with ATTRv amyloidosis. At the moment there is no clear signal that cancer patients have an increased risk besides the increased risk of their older age, but data is still accumulating [7, 8].

All patients with systemic amyloidosis should be informed of their vulnerability and encouraged to adhere to general measures to prevent infection, including social distancing, cleaning surfaces, washing of hands frequently, and limiting traveling and personal contacts. Also, impairments and shortages due to the current emergency should be taken into account in patient management, as well as expectations in end-of-life care.

These recommendations are made based on current understanding of SARS-CoV2 infection and must be interpreted and applied in the context of new data, as they become available.

Q1: Should we be changing indications for therapy in patients with AL amyloidosis?

- Indication for starting treatment is in most cases the detection of the systemic amyloidosis with severe disease burden for patients. Therefore, changing indications for treatment is not recommended, particularly in patients with clinically relevant heart involvement, since this will increase the risk of amyloid related morbidity and mortality. Because the delay in accurate diagnosis is already too long in many cases, initial treatment can rarely be delayed. However, in patients with organ involvement that has limited functional impact and early stage, treatment could be delayed for 8-12 weeks to get past the infection peaks. Second line and further treatments should be strongly individualized since patients with cardiac involvement can seldom wait, but other patient categories can possibly delay starting treatment for a few months.

Q2: Should we change our approach to therapy in patients with AL amyloidosis?

- Oral combinations should be preferred whenever possible. If available, proteasome inhibition with ixazomib could be an alternative to bortezomib. There are no data to compare Ixazomib with bortezomib in any disease setting, but in the current pandemic this substitution may be reasonable for some patients. Reduced doses of dexamethasone are advised.
- Proteasome inhibition increases risk with viral infection [9-11]. Alternative oral regimens, such as cyclophosphamide, thalidomide, and dexamethasone (CTD) and melphalan and dexamethasone (MDex) can be considered according to patient's characteristics and plan of future autologous stem cell transplantation.
- When access to hospital is necessary, less intensive schedules with less frequent administrations should be favored.

- Some institutions are not performing autologous stem cell transplant during the COVID-19 pandemic. In transplant candidates, when deep hematologic responses can be obtained with stem cell-sparing chemotherapy, transplant should be delayed.

Q3: Should we change therapies for non-SARS-CoV2 positive patients with AL amyloidosis who have already started treatment?

- The risk of SARS-CoV2 infection and of morbidity and mortality in systemic AL amyloidosis for various treatment regimens is unknown. There are currently no concrete data that suggests that cancer therapies should be ceased in patients on active treatment. However, treatment decisions require consideration based on patient's clinical status, degree of response, and risk of developing SARS-CoV2 infection.
- For patients who have already achieved a satisfactory response (i.e. CR, VGPR, or even PR + organ response) to therapy, a reduced number of cycles may be considered.
- In relapsed/refractory patients treated with IMiDs, once a satisfactory and sustained hematologic response is achieved, discontinuation of dexamethasone should be considered.
- In patients treated with daratumumab, earliest possible switch to monthly administrations is advisable. In addition, since clinical trials have been conducted with a fixed duration of daratumumab infusions, also stopping daratumumab infusions could be an option, if patients are beyond those time points and have achieved a satisfactory response. In those with adequate cardiac function a more rapid infusion after the first 2 administrations (at 90 minutes, 500 ml total volume) is advised to decrease time spent in the hospital. In non-nephrotic patients with hypogammaglobulinemia immunoglobulin replacement therapy should be considered.
- Specifically, for patients with an IgM-AL amyloidosis, it is recommended that maintenance rituximab be discontinued in case of underlying WM, because of the lack of evidence for survival benefit, and because of the increased risk of immunosuppression, and the requirement for travel.

Q4: In patients with AL amyloidosis should we change therapy to minimize visits? For example, changing to oral or less frequent regimens?

- Some patients may be eligible to receive up to a three-month supply of their oral medication; this approach, with labs obtained locally and telehealth visits may allow patients to self-isolate at home [12]. Attenuated chemotherapy dosage can be considered when appropriate to prevent neutropenia and the need for clinic visits for testing.
- Patients who are on "watchful waiting" may have visits delayed with telemedicine alternatives, with lab work obtained locally or delayed if risk is low. Home collection of

blood samples should be used, if this service is provided by laboratories with appropriate social distancing measures.

Q5: Should we change our approach to ATTR amyloidosis?

- Treatment for ATTR amyloidosis is not expected to increase the severity or mortality of COVID-19. However, patients with ATTR amyloidosis should be considered at increased risk if infected by SARS-CoV2 due to their organ involvement and need to travel for treatment and evaluations.
- Patients receiving subcutaneous or intravenous treatment should be enrolled in home care programs whenever possible. In previously untreated patients, initiation of oral treatment or subcutaneous/intravenous therapy in the context of home care programs, according to center and country policies could be considered.
- Traveling for treatment and evaluations should be reduced to a minimum, and telemedicine performed whenever possible.

Q6: Should we change our approach to supportive care?

- Consideration of a more liberal approach to antibiotic prophylactic regimens in consultation with Infectious Disease experts is recommended.
- Where indicated, routine vaccination against influenza and Pneumococcus should be continued.
- For patients with dialysis-dependent renal disease, measures to reduce the risk of COVID-19 in dialysis facilities have been recently reviewed and should be followed [13].

Q7: What about patients enrolled in clinical trials?

- National regulatory agencies have made general recommendations, and sponsors have issued trial-specific guidelines that should be followed.
- The inclusion of new patients should be carefully evaluated, balancing expected benefits and additional risks caused by the need of traveling to trial centers and the additional strain study participation puts on the health system of the specific country.
- Patients already participating in a trial might be maintained on study. Importantly, options to reduce clinic visits such as telemedicine, avoiding visits unless required for absolutely necessary safety assessment, use of local laboratories, and shipping investigational drugs to patients should be considered. Investigators should work with the ethics committees, sponsors and regulatory agencies to get waivers to minimize the frequency of visits.

Q8: Is serological testing for COVID-19 likely to be affected in patients with AL amyloidosis?

- Serological lab tests for COVID-19 analyze SARS-CoV2 specific IgM and IgG and will not be affected by circulating free lights chains and M protein.

- However, patients on daratumumab, rituximab or who have disease-related hypogammaglobulinemia might not be able to mount an immune response to SARS-CoV2, and there is a possibility of a false negative serological test even if they were exposed to the virus.

Q9: Should I screen all amyloidosis patients for SARS-CoV2 infection?

- The criteria and methods used to screen patients for COVID-19 vary from region to region and should be based on local government recommendations and guidelines.

Q10: What else can we do to help?

- Ongoing data collection and observations made during this pandemic may be of immense help in the future. If feasible, setting in processes to allow data collection during or after the acute period of the pandemic is crucial.
- The International Society of Amyloidosis has a wide network across the globe. Amyloidosis patients and advocates play an active role in various aspects of disease management. Their help should be harnessed in dissemination of knowledge and in advocating for patients.
- The International Society of Amyloidosis promotes a survey (https://redcap.smatteo.pv.it/redcap/surveys/?s=JKC4MTAYLX) to gather information on the course of COVID-19 in patients with amyloidosis.

Prepared and approved by: Y Ando, U Hegenbart, E Kastritis, SK Kumar, P Milani, MC Minnema, G Palladini, V Sanchorawala, SO Schönland, AD Wechalekar

Note: These recommendations are meant to assist clinicians in making decisions regarding treatment of patients with amyloidosis. Adherence to these recommendations will not ensure successful treatment in every situation. Furthermore, these recommendations should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biological behavior of the disease. These recommendations reflect the best available data at the time this document was prepared. The results of future studies may require revisions to the recommendations in this document to reflect new data.

References

1. Driggin, E., et al., *Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic.* J Am Coll Cardiol, 2020.
2. Ritchie, A.I. and A. Singanayagam, *Immunosuppression for hyperinflammation in COVID-19: a double-edged sword?* Lancet, 2020.
3. Mehta, P., et al., *COVID-19: consider cytokine storm syndromes and immunosuppression.* Lancet, 2020. **395**(10229): p. 1033-1034.
4. D'Antiga, L., *Coronaviruses and immunosuppressed patients. The facts during the third epidemic.* Liver Transpl, 2020.
5. Alberici, F., et al., *Management Of Patients On Dialysis And With Kidney Transplant During SARS-COV-2 (COVID-19) Pandemic In Brescia, Italy.* Kidney Int Rep, 2020.
6. Fernández-Ruiz, M., et al., *COVID-19 in solid organ transplant recipients: a single-center case series from Spain.* Am J Transplant, 2020.
7. Liang, W., et al., *Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China.* Lancet Oncol, 2020. **21**(3): p. 335-337.
8. Wang, H. and L. Zhang, *Risk of COVID-19 for patients with cancer.* Lancet Oncol, 2020. **21**(4): p. e181.
9. Smalls, D.J., et al., *Hepatitis B Virus Reactivation: Risk Factors and Current Management Strategies.* Pharmacotherapy, 2019. **39**(12): p. 1190-1203.
10. Marchesi, F., et al., *Cytomegalovirus infection in hematologic malignancy settings other than the allogeneic transplant.* Hematol Oncol, 2018. **36**(2): p. 381-391.
11. Morrison, V.A., *Immunosuppression associated with novel chemotherapy agents and monoclonal antibodies.* Clin Infect Dis, 2014. **59 Suppl 5**: p. S360-4.
12. Willan, J., et al., *Care of haematology patients in a COVID-19 epidemic.* Br J Haematol, 2020.
13. Kliger, A.S. and J. Silberzweig, *Mitigating Risk of COVID-19 in Dialysis Facilities.* Clin J Am Soc Nephrol, 2020.