# SUPPORTIVE CARE STRATEGIES DURING THE COVID-19 PANDEMIC

Due to the COVID-19 pandemic, there are different factors that might require changes in therapeutic and prophylactic supportive care interventions. All oncological treatment is a balance of risk and benefit. The presence of COVID-19 adds additional risk that needs to be considered when planning treatment and when pursuing diagnostic and treatment procedures. Intervention options that minimise clinic and chemotherapy visits are preferred. Selected patients are appropriately assessed by telehealth systems to avoid clinic visits. We must consider that there may be reassignment and shortages of resources such as blood products which may limit our supportive strategies. Furthermore, preventing urgent care visits to already crowded emergency departments with many infected patients has special priority at this difficult time. We discuss key aspects of prophylactic supportive care interventions in the following table. Some recommendations are broad and must be adapted to country- and hospital-specific resources and infrastructure.

The need and intensity of treating the malignant disease must be weighed against the possible higher risk of cancer patients of developing severe complications in the course of a SARS-CoV-2 infection. Some early Chinese reports indicated about a doubling of the mortality rate in patients with cancer (especially with lung cancer). Factors identified as playing a crucial role in other community-acquired respiratory virus (CARV) infections include duration of severe neutropaenia, lymphocytopaenia < $0.2x10^9$/L, and age >65 years (as a probable surrogate of co-morbidities and lesser reserves in case of severe stress). Most reports with SARS-CoV-2 infection indicate a significantly higher mortality rate for men. The roles of other concomitant illnesses and a high level of immunosuppression associated with many malignancies and treatments doubtless contribute to the greater risk for patients with cancer.

## Current adjustment recommendation by symptom

## (Expert opinion only, due to the urgency of the situation)

**Acute cerebellar syndrome**

- To lower the incidence of acute cerebellar syndrome very high doses of cytarabine treatment should be avoided if possible, especially in patients with renal impairment [1.5 g/m² instead of 3 g/m²]

**Anaemia**

- Up to now, there is no evidence of COVID-19 transmission via blood products
- In certain regions and a certain time, a possible shortage in blood products is expected
- To lessen symptomatic anaemia in patients with malignant conditions and receiving chemotherapy, ESA therapy should be considered as an option to avoid additional clinic visits. The risk of thrombosis should be considered, and one should consider symptoms rather than particular Hb thresholds. In individual patients, a Hb threshold of about 7 g/dl (4.35 mmol/l) should be considered
- Long acting ESA formulation might be a good choice in this situation
- It should be recognised that ESAs generally do not work quickly and, in most studies, result in a 1 to 1.5 g/dl (0.62 to 0.93 mmol/l) change
- In patients with severe anaemia-related symptoms (even at Hb levels above 7 g/dl (4.35 mmol/l)) and the need for immediate Hb and symptom improvement, the administration of RBC transfusions is the option of choice

**Bone complications**

- Withholding bone targeted agents should be considered in many situations during this pandemic period. If utilised as a parenteral intervention, the injection should be given during an already necessary visit rather than requiring a separate visit
- Patients should have a dental examination and, when feasible, complete invasive dental treatments before initiating a bone targeted agent. It should be recognised that dental services may be greatly reduced in many locations and may be limited to emergency dental interventions
    - In high-risk regions, patients might be seen in specialised centres for oral-maxillofacial surgery if usual dentist care is not possible, and if the specialists are open to this approach
- Patients receiving bisphosphonates for metastatic cancer can be safely changed to a 3-months interval
- The usual treatment interval of denosumab is every 4 weeks. As it is subcutaneously administered substance, it can be administered outside of the hospital
- Using oral bone targeted agents can also be considered
- Ensure vitamin D supplementation and adequate intake of calcium throughout treatment with bone targeted agents in order to avoid symptomatic hypocalcaemia

**Cytokine Release Syndrome (CRS)**

- The most common adverse event of CAR T-cell therapy is CRS, ranging from mild to severe symptoms whose treatment might require intensive-care measures. Therefore, a possible shortage of ICU capacities due to the treatment of patients with COVID-19

has to be strongly considered in the decision to use and in the planning of cellular therapy regimens

**Diarrhoea**

- It is important to recognise that 5-10% of patients with COVID-19 had diarrhoea as a symptom
- Patients should be made aware of the fact that clinical visits due to severe diarrhoea should not be delayed during this pandemic
- Patients undergoing therapy with a relevant risk of treatment-related diarrhoea (e.g. irinotecan, 5-FU, capecitabine, tyrosine kinase inhibitors, immune checkpoint inhibitors) should be specifically made aware of the risk of diarrhoea and of necessary basic measures (oral hydration, prescription of loperamide – to be used if needed, how to recognise warning symptoms)
- Physicians are recommended to follow the standard algorithm for the handling of therapy-induced diarrhoea: strongly consider hospital admission in patients with diarrhoea CTCAE grade 3-4 or lower stage with additional warning symptoms (e.g. nausea, emesis, cramps, fever, blood in the faeces)

**Fatigue**

- A well-structured exercise programme is an essential element in the therapy of fatigue syndrome. Many hospitals have therefore established specialised supervised training groups. Due to the restriction of group meetings, these training options should not be pursued at the moment. Patients should be encouraged to continue their exercise and should be advised through web-based training units or instructive booklets

**Febrile neutropaenia**

- Specifically, in patients with solid tumours not treated for cure, if possible, consider using regimens unlikely to induce febrile neutropaenia. There should be considerable evidence to support using regimens with greater neutropaenia risk which clearly outweighs today's considerable risk requiring emergency intervention
- Consider expanding the indication of G-CSF after chemotherapy to lower the risk of febrile neutropaenia. (The theoretical raised concern of acute respiratory failure due to G-CSF-induced leukocyte recovery in patients with pulmonary infections due to COVID-19 infection does not outweigh the benefit). However, one must recognise that this approach may require additional visits to the outpatient clinic
- Well documented and verified published criteria (see the MASCC febrile neutropaenia risk group stratifications, 14th April 2020, date last accessed) exist for the outpatient treatment of febrile neutropaenia in lower-risk group patients, with published randomised trials using oral antibiotics
- The use of antibiotics prophylaxis and/or prescription of stand-by antibiotics (to be used if needed) should be expanded in the current situation due to a possible risk of a delay to emergency visits for patients who develop fever (amongst other risks). Of

course, one has to bear in mind specific risks concerning multi-drug resistant bacteria in different regions

- The use of steroids should be critically reviewed and reduced if possible (see also "nausea and vomiting")
- According to the EMA recommendation from 13.3.2020 (independent of the COVID-19 pandemic): genetic testing of patients due to receiving a fluoropyrimidine in order to identify those with DPD deficiency is recommended (critical neutropaenia, diarrhoea, mucositis, etc.). Corresponding EMA link (9th April 2020, date last accessed)
- CDK4/6- or PARP-inhibitor-induced neutropaenia has not yet demonstrated a clear rise of associated viral infections

**Hypogammaglobulinaemia**

- Nevertheless, secondary immunodeficiency can represent an indication for immunoglobulin replacement therapy as a protection against collateral infections. The indication should be placed according to the existing guidelines and benefit should be weighed for the individual patient against the risk of frequent clinic visits

**Nausea and vomiting**

- A good strategy would be that, if there is the slightest doubt of the risk of emesis, *overprescribe* a generous antiemetic prophylactic regimen to lower the risk of additional clinical visits and suffering due to these symptoms. This may include – depending on the emetogenic potential and individual risk factors – the combination of a 5-$HT_3$-RA* plus a neurokinin$_1$-RA plus dexamethasone** (single dose on the day of treatment) plus olanzapine
- *5-$HT_3$-RA: may consider the long acting 5-$HT_3$-RA palonosetron due to its potential better efficacy in the delayed phase of CINV specifically when reducing/sparing the dexamethasone dose
- **Dexamethasone: the use of steroids should be critically reviewed A reduced dose of dexamethasone on day 1 without additional use on the following days should be considered even in highly emetogenic chemotherapy. A completely steroid-free antiemetic regimen should only be considered in individual patients strongly felt to be at increased risk with even a single dosing of dexamethasone

**Peripheral neurotoxicity (CIPN)**

Practical aspects of counselling:

- Risk assessment of falling: Reassurance and intensification of safety measures, e.g.
    - check floor condition – slippery, uneven, loose rugs, stairs
    - usage of a cane or walker if gait is unsteady

**Pulmonary toxicity**

- Due to the risk of severe complications of a SARS-CoV-2 infection in patients with pre-existing pulmonary damage, potential antineoplastic therapy-induced pulmonary toxicity has to be considered and (e.g. immune checkpoint inhibitors, bleomycin, radiation touching extensive lung area) should be administered with particular caution
- In case of respiratory symptoms, an early CT scan is recommended for detailed depiction of pulmonary infiltrates and differentiation from COVID-19 disease itself

**Thromboembolic events**

- Prophylaxis of thromboembolic events should be continued according to the existing guidelines. Patients should receive careful monitoring to prevent possible bleeding complications
- Patients with COVID-19 infections: possible changes in coagulation parameters and associated complications
    - disseminated intravascular coagulation (related to a worse prognosis)
    - thrombocytopaenia (in most cases mild, but cases of severe manifestation have been described)
    - seemingly higher risk of venous thromboembolism rate
- Patients hospitalised with a confirmed diagnosis of COVID-19 should receive prophylaxis of thromboembolic events using low molecular weight heparin or fondaparinux, or even unfractionated heparin in critically ill patients with significantly reduced kidney function. When direct oral anticoagulants are used, possible drug interactions with medications that are tested for use against COVID-19 have to be considered
- The role of full anticoagulation in severely ill patients with COVID-19 remains controversial at the time of this writing

**List of abbreviations**: 5-FU, 5-fluorouracil; CAR-T cells, chimeric antigen receptor T cells; CARV, community-acquired respiratory virus; CINV, chemotherapy-induced nausea and vomiting; CIPN, chemotherapy-induced peripheral neuropathy; CRS, cytokine release syndrome; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DPD, dihydropyrimidine dehydrogenase; EMA, European Medicines Agency; ESA erythropoietin-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; ICU, intensive care unit; MASCC, Multinational Association of Supportive Care in Cancer; PARP, poly ADP ribose polymerase; RA, receptor antagonist; RBC, red blood cell.