



Management of primary cutaneous lymphoma patients during COVID-19 pandemic: EORTC CLTF guidelines Maarten Vermeer

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Introduction to primary cutaneous lymphomas

During severe inflammatory *coronavirus infectious disease* (CoVID-19) pandemic and based on evidence on COVID-19 epidemiology, patients with primary cutaneous lymphomas (PCLs) have risk for developing complicated COVID-19 infections in consideration of their older age (majority above 60) and their potential underlying predisposing conditions (e.g. hypertension, diabetes).^{1,2,3} Moreover, PCL patients with aggressive biologic behavior should be carefully monitored according to guidelines for patients with neoplastic disease.^{4,5} The basic effort is to really protect patients from getting the virus according to CDC guidelines and on the suggestions made by hematology and oncology groups.

SARS-CoV-2 is a novel betacoronavirus first identified in China in winter 2019 as the cause of severe the respiratory tract infection and behaves like a new member of the community-acquired respiratory viruses (CARVs). The World Health Organization has confirmed COVID-19 (a shortened version of coronavirus disease 2019) as the name of the disease that SARS-CoV-2 infection causes. Similar to other CARVs, the clinical presentation can range from a- and oligosymptomatic to full-blown influenza-like illness and primary viral pneumonia will follow. Cancer patients with CARV-infections are prone to co-infections, and bacterial/fungal superinfections are the primary cause for CARV- associated mortality in cancer patients.⁶ In the absence of more specific data, potential risk factors for severe course of COVID19 disease should be assumed as for other CARV-infections: severe immunodeficiency, lymphopenia, long and profound neutropenia and older age. Severely immunosuppressed patients generally have a higher risk of developing complications in CARV infections and it should be assumed that cancer patients are at risk of a more severe course of COVID-19 as well. There are limited data on immunosuppressed hosts, but early published reports from China on the outcomes of patients with cancer infected with COVID-

19 indicated a 3.5 times higher risk of needing mechanical ventilation or ICU admission or dying compared with patients without cancer.³ The prognosis is bad for an oncology patient with late-stage disease or comorbid health conditions, such as heart or lung dysfunction, who acquires COVID-19 and requires mechanical ventilation.² According to a recent retrospective study from Wuhan, China, only one patient survived among 32 who were seriously ill with confirmed COVID-19 and required mechanical ventilation.²

PCLs are rare non-Hodgkins lymphomas, localized to the skin, without any extracutaneous involvement at the time of initial diagnosis. PCLs can originate either from T or B lymphocytes, called cutaneous T-cell lymphomas CTCL accounting for 75% of PCLs or cutaneous B-cell lymphomas (CBCL) accounting for 25% of PCLs. Mycosis Fungoides (MF) and Sezary Syndrome (SS), represent the commonest types of CTCLs deriving from skin-homing mature T-cells.⁷

Based on the WHO/EORTC classification⁸ PCLs are further categorized into 2 types: 1. indolent and 2. aggressive PCLs. The majority of CTCL and CBCL patients belong to the first group with indolent behavior; patients with aggressive PCLs belong to a group with a very low prevalence. The first group of indolent PCLs or low risk patients includes early MF (75% of all MF patients) and MF variants, lymphomatoid papulosis and CD30 positive anaplastic lymphoma, primary cutaneous acral CD 8 positive lymphoma, the provisional entities primary cutaneous CD4 positive T cell lymphoproliferation and indolent types of B-cell lymphomas such as marginal zone and follicular CBCLs. The second group of aggressive PCLs or high risk patients includes patients with advanced-stage MF (25% of all MF patients) and Sezary Syndrome (SS) patients, and rarest PCLs such as gamma/delta lymphoma, NK/T cell lymphoma, CD8 aggressive epidermotropic lymphoma, primary cutaneous diffuse large B-cell lymphoma, leg type; primary cutaneous diffuse large B-cell lymphoma, intravascular B-Cell Lymphoma and hematologic precursor neoplasm.

MF is the most common PCL and is initially characterized by patches and infiltrated plaques on the skin which eventually evolve into tumors.⁹ On the other hand, SS is the leukemic variant of MF, characterized by erythroderma, lymphadenopathy and the presence of a malignant T-cell clone in the peripheral blood and the skin.⁹ The median age at diagnosis ranges from 52 to 62 years and all studies had a male predominance of 1.6 (male:female ratio

6:4) in accordance with previous reports.¹⁰⁻¹¹ MF is a slowly developing, low-grade lymphoma with a progressive accumulation of atypical lymphocytes in the skin's epidermis, leading from patches and plaques to a more aggressive disease with the typical ulcerated nodules, and in later phases with migration of T-cells to lymph nodes, peripheral blood and visceral organs. Overall survival correlates with stage, advanced stages of MF and SS are comprised of stages IIB-IVB and are associated with a worse prognosis than early-stage disease: patients with stage I MF may have a long survival whereas survival is poor in advanced MF and SS with median survival quoted at about 3 years and a 5-year overall survival of between 10% and 20%.¹⁰ Most patients die of opportunistic infections due to an incompetent immune system.¹²⁻¹⁶ There is a great variation in survival within the stages of MF and SS and the importance of poor prognostic indices outside the staging system has been recognized in determining prognosis within the same stage, ie Survival in stage IB MF is significantly reduced in up to one in five patients, with death within 5 years of diagnosis.¹⁷⁻¹⁸ The Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIP) study is a global prospective effort collecting clinical, pathological, genotypic, treatment, and health-related quality of life (HRQoL) data on all stages of MF and SS with the aim to develop a prognostic index to stratify patients for better management decisions and to improve survival. Identifying risk factors for poorer survival may allow individualized treatment choices. In PROCLIP, factors being tracked as possible poor prognostic markers in stage IB include folliculotropic MF (FMF; recorded in 24.8% of patients with stage IB MF), large cell transformation (LCT) in skin (which is defined as >25% overall or microscopic nodules of atypical lymphocytes being greater than normal size [recorded in 1.7% of patients with stage IB MF]), low level blood involvement with circulating aberrant lymphocytes (typically CD4+, CD7-, or CD26-) between 250 and 1000 IU as defined by B1 (recorded in 26.1% of patients with stage IB MF), and raised serum lactate dehydrogenase (LDH; recorded in 8.9% of patients with stage IB MF).¹⁸

In clinical practice, treatment choice depends on the type and biologic behavior of the lymphoma and is adapted to clinical stage.¹⁹ For patients with advanced disease, prognosis is still grim, and only for a highly select subset of patients, prolonged survival can be achieved with allogeneic stem cell transplantation (alloSCT).¹⁹ Skin-directed therapies are still the most appropriate option for early-stage MF, and most patients in stage IA will have a normal life expectancy but morbidity from skin symptoms such as itch and pain, emotional disturbance from unsightly lesions and dealing with a non curable disease reduced function ie

from lesions on the hands can negatively impact on quality of life.²⁰ Low risk patients especially those that do not receive systemic treatment are not more susceptible to infections than the general population. Patients in advanced stages with a defective immune system are more susceptible to opportunistic infections and probably to a more severe course of coronavirus infection. Although CTCL diagnosis does not represent a predisposing factor to viral infections and most of CTCL patients have an indolent disease, factors such as older age, comorbidities, multiple previous immunosuppressive treatment and advanced/aggressive disease are important risk factors to consider in this group of patients during the COVID pandemic. In addition lymphopaenia is seen in around 10% of all stages of MF, furthermore the number of functioning CD4 cells may be further reduced as the clonal neoplastic CD4 cells may be non-functioning (ref). Lymphopaenia is a poor prognostic marker at presentation of COVID-19 and may be assumed that pre-existing lymphopaenia may predispose to a worse infection with COVID-19.²¹

General Guidelines for all patients with PCL

The basic effort is to really protect patients from getting the virus according to CDC guidelines.

HOTLINE FOR QUESTIONS. For all patients each PCL center should implement a hot line to answer patients questions.

SELF ISOLATION. Patients should be in self isolation to avoid the risk of infection as most people are doing in order to avoid contamination with COVID. Education that COVID-19 is droplet spread and may live for hours even days on some surfaces. Avoid touching face with hands, observe strict hand-washing.²²

Strict isolation and social distancing to 2 meters is of course very important for all patients to avoid contamination with COVID. Especially late stage disease or aggressive lymphomas who are more immunosuppressed and susceptible to infections.

HAND HYGIENE AND SKIN INTEGRITY. For all patients hand hygiene is important as well as skin treatment to avoid open wounds. The best way to protect in the short-term is to

stay at home to the extent possible, practice social distancing and avoid touching face/wash hands frequently if patients have to go out (and should not go out if sick).

Masks must be worn if patients have flu-like symptoms all time outside home. To protect rest of people, and if patients visit the hospital for treatment, are in the middle of infusions and have to complete their treatment cycle.

The use of protective masks is what now seems to be considered a very critical issue in order to reduce the rate of infection and everybody should be using them when they go out or are among other people anywhere.

If patient comes with COVID suspicion (fever, cough, fatigue), do first a PCR test and isolate the patient waiting for the result. In most countries a triage medicine is performed before patients enter the hospital, patients with any symptoms and reason for an inpatient service are screened by smears. If the test is negative the patient is taken by dermatology for treatment. If test positive, priority is that the patient is handled by infectious diseases department. In case of lung disease which might be acute and life threatening, CTCL can then be treated following recovery from the infection.

A. The indolent lymphomas or low risk patients which are on topical or systemic treatment, should be seen by teledermatology for their follow up and receive their prescriptions by mail to avoid coming to hospital. We can prescribe electronically. Patient go with his personal health card to the pharmacy and get the treatment

In case of PUVA and NB UVB treatments the decision should be made depending on the hospital situation. As most of the Photobiology Units have been closed in several centres, phototherapy might be not available and postponed.

These patients could be treated with Topical potent steroids or/and Ledaga available in some European countries. In France the drug will be soon available not only in hospital pharmacy but also in local pharmacy.

For patients with indolent disseminated B cell lymphoma with an indication to receive Rituximab, the treatment is not urgent and can be postponed for 2 months, although it is not demonstrated that rituximab is possibly increasing the risk of severe COVID disease (rituximab reduces B cells but plasma cells maintain production of immunoglobulins).

B. For late stage disease or aggressive lymphomas:

PCL patients with controlled underlying disease have fewer infections than untreated patients, therefore patients with active malignant disease should be treated accordingly and timely to prevent a worsening in outcome. As with hematology patients⁴ uncontrolled malignant disease should be avoided and life-threatening malignancy needs treatment, especially if there is relevant curative potential. This includes systemic therapy or radiation.

CTCL patients in this group are older, more immunosuppressed and susceptible to infections, usually die from sepsis and could be probably more susceptible to more severe course of coronavirus. These are severely immunosuppressed patients who generally have a higher risk of developing complications in CARV infections and it should be assumed that cancer patients are at risk of a more severe course of COVID-19 as well. In the absence of more specific data, potential risk factors for severe course of the disease should be assumed as for other CARV-infections: severe immunodeficiency, lymphopenia, long and profound neutropenia and older age.(210)

Clinicians should also be aware that cancer patients generally shed CARV longer than immunocompetent people²³ and this is probably true for this novel coronavirus as well. Patients with advanced disease are immunosuppressed even if not on systemic treatment and should be considered as high risk population for coronavirus infection according to their comorbidities, older age and lymphopenia. .

Patients in this group should

1) Continue receiving their medication such as infusions for advanced lymphoma patients with Brentuximab Vedotin (CD30 antibody), Gemcitabine , Rituximab (CD20 antibody), and Extracorporeal Photopheresis. At the moment, there is no evidence in cancer patients receiving checkpoint inhibitors that the personal risk increases.

2) Maintain a possibility of IV treatments in COVID negative zones for late stage and aggressive lymphomas (for urgent chemotherapy, or monoclonal antibodies)
Discuss for each patient the benefit/risks of treatments.

3) Do not prophylactic interrupt continuous therapies. If the disease is in partial remission or stable, especially for patients with old age and/or comorbidities it can be preferable to stop treatments or at least decrease the frequency of infusions (to be discussed)

Patients might be worried about their treatment :

4) Some patients may ask about the possibility to stop methotrexate treatment (possibly increasing the risk of severe COVID disease although not demonstrated). To be discussed depending on indication and evolution

5) Mogamulizumab (CCR4 antibody) induces lymphopenia and possibly increasing the risk of severe COVID disease, although not demonstrated. Some therapies associated with significant cytopenias and toxicities could be assumed a risk factor for adverse outcome of COVID-19 such as Alemtuzumab (CD52 antibody) which is highly immunosuppressive and polychemotherapy.

6) Other systemic treatment used in CTCL such as IFN-2a or Bexarotene should be continued during COVID pandemic.

7) Rituximab or corticosteroids (systemic prednisone or prednisolone), even if stopped, it takes sometime for their immune system to return to normal levels

Risks related to the trials especially during the COVID crisis

It is important to consider that drugs associated with hypersensitivity phenomena may aggravate COVID-19-induced hypersensitivity pneumonitis.²⁴ Interruptions of these therapies may seem prudent in patients presenting with symptoms. Immune checkpoint inhibitors are currently on clinical trials for the treatment of MF/SS (EORTC clinical trial PARCT 1652) and immunotherapy with PD-1 and PDL-1 inhibitors poses the risk for autoimmune events, including pneumonitis. The treatment for autoimmune events often

requires the use of high dose corticosteroids. These two aspects should be carefully considered when treating patients with immune checkpoint inhibitors during the COVID-19 crisis.

All symptomatic family members or those at high risk of early infection with SARS-CoV-2 should stay away from patients with active malignant disease or currently on treatment regardless of risk of corona.⁴ The use of protective masks is what now seems to be considered a very critical issue in order to reduce the rate of infection. Particular care should be given to >70 years and contact with children must be avoided.⁴ Patients should be advised regarding the importance of good general health to stop smoking, reduce weight loss if obese, exercise, ensure a sufficient supply of vitamins like vitamin C and D, and the treatment of any iron-deficiency.⁴

In conclusion, the majority of patients with PCLs have an indolent course and should continue on treatment, avoid hospital visits and be assessed by teledermatology. CTCL diagnosis does not represent a predisposing factor to viral infections and most of CTCL patients have an indolent disease. However physicians should be cautious with patients with aggressive PCLs and advanced CTCL. More specifically patients with advanced CTCL should be carefully handled especially those with adverse prognostic factors such as older age and advanced or aggressive disease in addition to risk factors to COVID infections such as comorbidities and multiple previous immunosuppressive treatment. Laboratory markers such as lymphopenia may present in a group of these patients mainly caused by therapeutic agents should also be considered as an adverse factor for COVID infection as well as agents that might cause hypersensitivity phenomena which should be cautiously administered.

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