



Primary cutaneous lymphomas and Coronavirus disease-2019: A critical overview of primary cutaneous lymphoma management in pandemic

Primer kutanöz lenfomalar ve Koronavirüs hastalığı-2019: Pandemide primer kutanöz lenfoma yönetiminin gözden geçirilmesi

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Abstract

Coronavirus disease-2019 (COVID-19) is a serious cause of respiratory tract infection, and its severe course has been associated with some risk factors, including malignancies and immunosuppressive treatments. Primary cutaneous lymphomas (PCL) are a heterogeneous group of immune system neoplasms, which are subclassified as indolent and aggressive types according to their survival rates. PCL treatment ranges from skin-based therapies to systemic treatments, of which immunosuppressive effects occur in some. During the COVID-19 pandemic, patients with PCL should be protected from possible COVID-19 complications, and the optimal treatment should be provided to control the disease taking into account the treatment-related risks. Therefore, recommendations about the management of patients with PCL during the COVID-19 pandemic were overviewed in light of the literature. Topical treatments can generally be considered low-risk therapies and can be continued without interruption. Phototherapy, skin radiotherapy, and total skin electron beam therapy increase the risk of COVID-19 exposure due to hospital visits. Moderate-risk therapies like interferons, systemic retinoids, methotrexate, and systemic corticosteroids might be used with caution. Advanced-stage patients with COVID-19 related comorbidity and who previously received immunosuppressive therapy should be carefully evaluated. Biological agents and systemic chemotherapeutics, which are considered high-risk, should not be delayed when needed. However, increasing intervals between treatments or switching to alternative therapies may be preferable in stable diseases. Most importantly, all patients with PCL should be ensured to comply with general protection measures as long as the pandemic continues.

Keywords: Primary cutaneous lymphoma, COVID-19, management

Öz

Koronavirüs hastalığı-2019 (COVID-19), solunum yolu enfeksiyonunun ciddi bir nedenidir ve şiddetli seyri, maligniteler ve immünoşüpresif tedaviler gibi bazı risk faktörleriyle ilişkilendirilmiştir. Primer kutanöz lenfomalar (PKL), sağkalım oranlarına göre indolent ve agresif tipler olarak sınıflandırılan heterojen bir immün sistem neoplazmaları grubudur. PKL'lerin tedavisi, deriye yönelik tedavilerden sistemik tedavilere kadar uzanır ve bunların bazılarının immünoşüpresif etkileri vardır. COVID-19 salgını sırasında, PKL'li hastalar olası COVID-19 komplikasyonlarından korunmalı, tedaviye bağlı riskler de dikkate alınarak hastalığı kontrol altına almak için optimal tedavi sağlanmalıdır. Bu bağlamda, COVID-19 pandemisi sırasında PKL yönetimi ile ilgili önerileri literatür ışığında gözden geçirdik. Topikal tedaviler genellikle düşük riskli tedaviler olarak

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düşünülebilir ve kesintisiz olarak devam ettirilebilir. Fototerapi, deri radyoterapisi ve total deri elektron ışınlanması tedavileri, hastane ziyareti gerektirdiği için COVID-19'a maruz kalma riskini artırır. Interferonlar, sistemik retinoidler, metotreksat ve sistemik kortikosteroidler gibi orta riskli tedaviler dikkatle kullanılabilir. COVID-19 ile ilişkili komorbiditeye sahip ileri evre hastalar ve daha önce immünoşüpresif tedavi almış hastalar dikkatlice değerlendirilmelidir. Yüksek riskli olduğu düşünülen biyolojik ajanlar ve sistemik kemoterapötikler gerektiğinde geciktirilmemelidir. Bununla birlikte, hastalık stabil ise, tedaviler arasındaki aralıkların uzatılması veya alternatif tedavilere geçiş tercih edilebilir. En önemlisi, PKL'li tüm hastaların pandemi devam ettiği sürece genel koruma önlemlerine uyması sağlanmalıdır.

Anahtar Kelimeler: Primer kutanöz lenfoma, COVID-19, tedavi

Introduction

Coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)^{1,2}. It can be clinically asymptomatic or cause severe viral pneumonia, which can lead to respiratory failure and even death¹. Some patient groups might be more susceptible to this infection due to their risk factors, including their disorders and relevant medications^{3,4}. One of these vulnerable patient groups may be claimed as patients with primary cutaneous lymphoma (PCL). They seem to be at risk of developing complications during COVID-19 as they are usually older with comorbidities and are receiving immunosuppressive therapy to provide long-term disease control. Additionally, the uncontrolled disease of patients with PCL correlates to a higher incidence of infection as the disease itself may cause an immunosuppressive state. Thus, during the COVID-19 pandemic, patients with PCL should be protected from possible COVID-19 complications and optimal balance should be provided while managing the disease. Therefore, recommendations regarding the management of patients with PCL during the COVID-19 pandemic were overviewed in light of the literature.

Stratification of PCL according to their risks

PCL is a heterogeneous group of immune system neoplasms that are characterized by T-lymphocyte, B-lymphocyte, or natural killer (NK) cell proliferation and their orientation to the skin⁵. Of PCL, 73% are cutaneous T-cell lymphoma (PCTL), 22% are cutaneous B-cell lymphoma (PCBL), and the remainder is other rare cutaneous lymphomas, such as NK-cell neoplasms⁶. They are categorized into indolent and aggressive types based on the World Health Organization/European Organization for

Research and Treatment of Cancer (EORTC) classification⁵. Additionally, the United States Cutaneous Lymphoma Consortium classified them into subgroups according to risk as low, intermediate-low, intermediate-high, and high⁷. The risk groups of PCL were gathered under a single table taking into account the risk of COVID-19 complications (Table 1)^{5,7}.

The risk of COVID-19 infection of patients with low-risk, especially those that do not receive systemic therapy, is thought to bear the same risk as to the general population. However, patients with advanced disease are more susceptible to opportunistic infections and probably to a more severe COVID-19 infection since their immune systems are already defective even if they do not receive systemic therapy⁸.

Mycosis fungoides (MF), which is the most common type of PCTL, have an indolent course in the majority of patients. Still, factors like older age, comorbidities, immunosuppressive therapies, advanced stage, and aggressive disease are important risk factors to consider in this patient group during the COVID-19 outbreak⁸.

Recommendations for PCL management during the COVID-19 pandemic

1. General protection measures

First of all, patients with PCL should be ensured to comply with general protection measures as long as the pandemic continues. The risk of viral transmission was shown to reduce when precautions are taken against contamination through droplets and contamination from surfaces⁹. Patients should be informed that COVID-19 spreads by droplets and the best way of protection are to wear a mask around others. They should be warned to wash their hands very frequently and duly, not to touch their face with hands, not to spend time in crowded environments, and not to approach anyone >2 m. They should also be

Table 1. The risk groups of primary cutaneous lymphomas^{5,7}

Indolent PCLs		Aggressive PCLs	
Low risk	Low-moderate risk	Moderate-high risk	High risk
MF stage IA	MF stage IB (extensive patches/plaques)	MF stage IIB (tumors)	MF stage IV
MF stage IB (patches or limited BSA)	MF stage 2A (reactive LAP)	MF stage III (erythrodermic)	Transformed MF
Pagetoid reticulosis	Folliculotropic MF	PC diffuse large B-cell lymphoma, not leg-type	Sézary syndrome
Lymphomatoid papulosis	Granulomatous MF	-	PC CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
PC CD4+ small/medium T-cell lymphoproliferative disorder	Granulomatous slack skin	-	PC gamma/delta T-cell lymphoma
PC Acral CD8+ T-cell lymphoma	PC anaplastic large cell lymphoma	-	Extranodal NK/T-cell lymphoma
PC marginal zone B-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	-	PC diffuse large B-cell lymphoma, leg-type
PC follicle center B-cell lymphoma	-	-	-

PCL: Primary cutaneous lymphoma, MF: Mycosis fungoides, BSA: Body surface area, LAP: Lymphadenopathy, PC: Primary cutaneous

informed about skincare and how to avoid traumas that could disrupt the integrity of the skin⁸.

2. Skin-directed therapies

Skin-directed therapies that are used in PCL were summarized in Table 2, and the risk categories regarding COVID-19 complications for each treatment option were noted.

The majority of patients with MF present with limited disease and are preferentially treated with skin-directed therapies. Skin-directed therapies are generally considered low-risk therapies for COVID-19 complications. The United States Cutaneous Lymphoma Consortium and EORTC Cutaneous Lymphoma Task Force recommend topical therapies as initial treatment in patients with low-risk^{7,8}, and low-risk therapies that can be used at home should be continued for all patients (Table 2).

Phototherapy is a low-risk therapy; however, the exact risk of the spread of SARS-CoV-2 through phototherapy units is still unknown. It may increase infection exposure due to hospital admission, thus experts subclassify phototherapy in the high-risk category⁷. Some countries temporarily closed phototherapy units during the peak of the pandemic to prevent in-hospital viral spread by outpatients or because some dermatological units were converted into COVID-19 treatment zones¹⁰. A study evaluated the disease status of patients who stopped receiving phototherapy and revealed that 95% of patients who stopped phototherapy for any reason reported a disease status worsening, and determining the number of patients who avoided SARS-CoV-2 infection because of this decision is difficult¹¹.

Phototherapy is an important treatment option for cutaneous T-cell lymphomas, and the decision of performing psoralen and ultraviolet A or narrowband ultraviolet B treatments in hospitals should be

made based on the hospital feasibility and COVID-the prevalence in that specific location, considering individual factors for each patient after a risk/benefit assessment⁸. In hospitals, where phototherapy units are available, a fewer number of patients than usual can be accepted with longer appointment intervals on the same day. While using phototherapy units during the pandemic, some special safety measures should be taken for the safety of patients and healthcare professionals¹²⁻¹⁴.

Before performing phototherapy, all patients should be evaluated for COVID-19-related symptoms, and in case of COVID-19 suspicion, the treatment of the suspected patient should be postponed. All patients should apply hand sanitizer upon entering and leaving the phototherapy unit and wear facial masks during the phototherapy, except for total body phototherapy treatment. Patients should be advised to bring a separate bag to put their clothes in before entering the phototherapy unit. Additionally, patients should be informed that at the end of each session they can disinfect their UV protective glasses following the manufacturer's recommendations¹²⁻¹⁴. Without specific recommendations, the glasses can be disinfected using wipes that contain 70-90% ethyl alcohol¹⁵.

The cleaning staff who works in coordination with the infection committee should be specifically trained on how to professionally clean phototherapy units. The phototherapy units should be ventilated for at least 15 min after each patient, and the floor of the units and the surfaces that were touched by the patients should be disinfected following the manufacturer's instructions¹²⁻¹⁴. Without specific recommendations, disinfectants containing quaternary ammonium (following the product label for use and dilution) can be used¹⁵. Bleach and alcohol should not be preferred as the former creates corrosion on surfaces and the latter causes toxicity when used on

Table 2. Skin-directed therapies^{8,9}

Skin-directed therapies	Mechanism of action
Low-risk	
Moisturizers	Restore skin barrier and reduce microorganism colonization
Diluted vinegar or bleach soaks/baths	Reduce microorganism colonization
Topical corticosteroids	Induce apoptosis of lymphocytes and prevent binding of lymphocytes to the endothelium
Mechlorethamine gel/ointment ^a	Alkylating chemotherapeutic agent Causes apoptosis of malignant cells
Topical imiquimod	Induces Th1 cytokines and causes apoptosis of malignant cells
Topical retinoids	
Bexarotene	RXR receptor agonist. Induces apoptosis of malignant cells
Tazarotene	RAR receptor agonist. Provides antiproliferative and anti-inflammatory activity
Home narrowband UVB phototherapy	Provides anti-proliferative and anti-inflammatory activity and causes apoptosis of T-cells
Moderate-risk	
Topical carmustine ^b	Alkylating chemotherapeutic agent Induces apoptosis by crosslinking to DNA and RNA
High-risk	
Office-based phototherapy (nbUVB and PUVA) ^c	Provides antiproliferative and anti-inflammatory activity and causes apoptosis of T-cells
Skin radiotherapy ^c	Causes death of tumoral cells by damaging DNA
Total skin electron beam therapy ^c	Causes death of tumoral cells by damaging DNA

^a: Not available in Turkey. ^b: Myelosuppressive effect may occur due to systemic absorption. Can be used if involvement is <3% of body surface area. Maintenance therapy is contraindicated. ^c: The risk increases due to the frequency of hospital visits and the risk of Coronavirus disease-2019 exposure. nbUVB: Narrowband ultraviolet B, PUVA: Psoralen and ultraviolet A

large surfaces. The phototherapy units should be re-ventilated after disinfection.

Skin radiotherapy and total skin electron beam therapy also increase the risk of COVID-19 exposure due to frequent hospital visits, as in office-based phototherapy⁷. Cutaneous anaplastic large cell lymphoma and low-risk PCBLs are usually locally treated with surgical excision or radiotherapy. Thus, continuing or postponing these treatments should be individually evaluated⁷.

3. Systemic therapies

Systemic therapies that were used in PCL were summarized in Table 3, and categories in COVID-19 complications of each treatment option were noted.

Moderate and high-risk therapies are required for the management of advanced and aggressive forms of cutaneous lymphomas. The well-controlled disease is associated with fewer infections, but treatment-based risks may overshadow this good outcome, thus the issue of how to use these drugs during the COVID-19 pandemic arises. Firstly, all treatment decisions should be made considering the benefits and risks of treatments individually for each patient. The United States Cutaneous Lymphoma Consortium stated that the initiation of moderate-risk therapies can be delayed for a short time using low-risk therapies, and moderate-risk therapies can be continued in patients who are already using them; however, individual dose adjustments may be considered (Table 3)⁷. The benefits of moderate-risk systemic treatments, such as interferon alfa-2 or bexarotene, generally overcome the risks in case of potential COVID-19 infection, thus they can be continued during the

COVID-19 outbreak. In patients who use high-risk therapies, retinoids or interferons can be preferred instead of high-risk therapy for the short-term as a bridge therapy, and increasing the doses of retinoids and/or interferons can be individually considered^{7,8}.

Concerns arise that methotrexate may increase the risk of COVID-19 complications due to its immunosuppression effects although it is not proven. Thus, decreasing the dose or increasing the intervals between treatments may be considered. Additionally, dose reduction or switching to low-risk therapies should be considered in patients who use systemic corticosteroids since it takes a while for the immune system to return to normal levels after stopping systemic corticosteroids^{7,8}.

High-risk therapies cannot be directly prescribed by dermatologists in Turkey, and they are usually applied by hematologists/oncologists. However, this study might contribute to the decision process of using high-risk therapies by sharing our opinions with our colleagues during consultation. High-risk therapies, in addition to their potential risks, like immunosuppression, may increase the COVID-19 exposure by requiring hospital travel. However, patients with active, advanced, and aggressive malignancies should be treated without delay since uncontrolled malignancies alone cause susceptibility to infections and worse outcomes⁸. Thus, high-risk therapies should be used only in high-risk patients, considering the additional travel risk⁷. The ongoing high-risk therapies of patients with advanced PCL should not be prophylactically stopped⁸. However, with stable or in partial remission diseases, increasing intervals between treatments or switching to alternative therapies may be preferable, especially in older patients with comorbidities^{7,8}. Allogeneic stem cell transplant

Table 3. Systemic therapies^{8,9}

Systemic therapies	Mechanism of action	Risk	Notes
Moderate-risk			
Interferons (alpha or gamma) ^a	Activates antitumor cytolytic cells (NK and T-cell), inhibits the growth of malignant T-cells, and increases Th1 cytokine response		
Retinoids^b			
Bexarotene	RXR receptor agonist Regulates biological response and induces apoptosis of malignant cells		
Acitretin	RAR receptor agonist Shows anti-inflammatory and antiproliferative activities		
Methotrexate	Stops cell division by inhibiting DNA synthesis, and shows anti-inflammatory and antiproliferative activities		
Systemic corticosteroids	Reduces proinflammatory cytokines and inflammatory cell migration		
Vorinostat ^c	Histone deacetylase enzyme inhibitor. Induces apoptosis		
High-risk			
Extracorporeal phototherapy ^d	Causes apoptosis of circulating malignant lymphocytes and induces Th1 cytokines		
Pralatrexate ^e	Stops cell division by inhibiting DNA, RNA, and protein synthesis		
Romidepsin ^e	Histone deacetylase enzyme inhibitor. Induces apoptosis		
Mogamulizumab ^e	Anti-CCR4 antibody. Causes antibody-dependent cellular cytotoxicity leading to the death of malignant cells		
Brentuximab vedotin ^e	Anti-CD30 antibody. Induces apoptosis		
Gemcitabine ^e	Stops cell division by inhibiting DNA synthesis		
Alemtuzumab ^{e,f}	Anti-CD52 antibody. Causes antibody-dependent cellular cytotoxicity leading to the death of malignant cells		
Other chemotherapies ^{e,f} (CHOP or fludarabine)	Stops cell division by inhibiting DNA synthesis		
Rituximab	Anti-CD20 antibody. Causes mature B-cell apoptosis		

^a: Not available in Turkey for a while. ^b: Do not cause immunosuppression. ^c: Not available in Turkey. ^d: The risk increases due to the frequency of hospital visits and the risk of COVID-19 exposure, Do not cause generalized immunosuppression. ^e: Can be applied by hematologists/oncologists in Turkey. ^f: They are not recommended as they cause significant cytopenia. CHOP: Cyclophosphamide, hydroxyrubicin, vincristine, prednisone

and cyclophosphamide, hydroxyirubicin, vincristine, prednisone, alemtuzumab, and fludarabine treatment are not recommended since they lead to pronounced cytopenia, which is a well-known risk factor for COVID-19 complications^{8,16,17}. Alternative therapies with lower risks should be used instead⁷.

No significant evidence was found for the increased risk of severe COVID-19 infection following rituximab; however, some case reports stated that rituximab outcomes on COVID-19 were severe in patients with systemic lymphoma/leukemia. Additionally, persisting viremia¹⁸, COVID-19 virus reactivation¹⁹, and prolonged COVID-19-associated pneumonia²⁰ have been associated with rituximab and its resultant B-cell depletion. Rituximab treatment is not urgent for patients with indolent disseminated B-cell lymphoma. Thus, it can be delayed for up to 2 months⁹. However, for patients with aggressive B-cell lymphoma, rituximab treatment should be continued during the pandemic²¹.

4. Inpatient clinics

At the beginning of the pandemic and at the peak times, inpatient clinics were reorganized and most of the beds were reserved for patients with COVID-19. In most dermatology inpatient clinics, only a few beds are reserved for urgent dermatological cases^{22,23}. Therefore, the number of hospitalized patients was observed to dramatically decrease compared with the number of hospitalizations in the same period in previous years²³. Unfortunately, the delay in hospitalization and treatment of people with chronic diseases and malignancies played a role in the increased number of deaths during the pandemic period^{24,25}. Therefore, in all treatment decisions, patients in need for hospitalization should be individually evaluated and necessarily hospitalized by providing appropriate conditions. Before a hospitalization, patients should be questioned about their state of health and any contact with patients having COVID-19 and should be tested for COVID-19 to ensure their status²². Additionally, patients should be encouraged to wear masks and keep them on throughout the whole visit.

5. Vaccination against COVID-19

Currently, cutaneous lymphoma-specific information regarding vaccinations was unavailable. Recommendations are based on experts' opinions due to the limitations in prospective data in the vaccination of patients with active malignancy. The National Comprehensive Cancer Network COVID-19 Vaccination Advisory Committee strongly suggests that COVID-19 vaccines should be given to all patients with cancer, as well as household contacts (≥ 16 years of age) and caregivers when they are eligible to receive the vaccine. Further, the committee has no preference for any of the approved vaccines²⁶. Australia and New Zealand have achieved excellent community control of COVID-19 infection. The Hematology Society of Australia and New Zealand and infectious diseases specialists have collaborated on a consensus position statement regarding COVID-19 vaccination in patients with hematological disorders including lymphomas²⁷. The Centers for Disease Control and Prevention recommends for those 12 years and older get a COVID-19 vaccine, which includes people with underlying medical conditions such as cancer²⁸. Large cohort studies revealed that patients with cancer are at high-risk for COVID-19 and vaccine trials have revealed that vaccines decrease the incidence of COVID-19 disease and complications; however, data suggest that vaccines may prevent SARS-CoV-2 infection and subsequent transmission risk are limited²⁹. Therefore, even if vaccinated, patients and close contacts

should continue to wear masks, maintain social distancing guidelines, and follow other recommendations for COVID-19 prevention.

The key principles are as follows:

1. Individuals with active cancer or those with active, recent (<6 months), or scheduled cancer treatment should be considered the highest priority to receive one of the currently available COVID-19 vaccines.
2. A history of cancer is unknown in increasing the risk for severe COVID-19. People with a history of cancer treatment may want to discuss their concerns about COVID-19 with their doctors.
3. Data on dual vaccination are unavailable, thus COVID-19 vaccines should be prioritized over other needed vaccines. A 14-day interval between COVID-19 vaccines and other approved vaccines is recommended.
4. For patients who have already started disease-specific therapies, therapy discontinuation at the time of vaccination is generally not recommended.
5. Some evidence pointed that patients undergoing cancer treatment or who are somehow immunocompromised may have a poorer vaccine response. Thus, delaying vaccination may be considered until immunosuppressive therapy is reduced and/or based on immunophenotyping of T-cell and B-cell immunity.
6. If possible, patients should be vaccinated 14 days before chemotherapy, cellular therapies, or T- or B-cell depleting therapies, but this should not delay urgent treatment.
7. Delaying vaccination for at least 3 months after B-cell-depleting therapy or stem cell transplantation is appropriate.
8. The efficacy of COVID-19 vaccines, particularly in patients with cutaneous lymphoma is unknown, thus vaccination in these patients should not replace other public health measures.

Conclusion

The majority of patients with PCL have an indolent course. Thus, low-risk therapies can be continued without interruption, and moderate-risk therapies might be used with caution. However, patients with advanced-stage COVID-19-related comorbidity and patients who previously received immunosuppressive therapy should be carefully evaluated. Most importantly, all patients with PCL should be ensured to comply with general protection measures as long as the pandemic continues. COVID-19 vaccines should be given to all patients with cancer, as eligible. These recommendations should be considered in the context of individual needs of patients, hospital resources, and COVID-19 outbreak prevalence in that specific location.

Ethics

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Authorship Contributions

Surgical and Medical Practices: S.Ö., A.B., S.Y., D.B., H.Ş., N.O., Concept: S.Ö., A.B., S.Y., D.B., H.Ş., N.O., Design: S.Ö., A.B., S.Y., D.B., H.Ş., N.O., Data Collection or Processing: S.Ö., A.B., S.Y., D.B., H.Ş., N.O., Analysis or Interpretation: S.Ö., A.B., S.Y., D.B., H.Ş., N.O., Literature Search: S.Ö., A.B., S.Y., D.B., H.Ş., N.O., Writing: S.Ö., A.B., S.Y., D.B., H.Ş., N.O.

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