



Pandemic medicine: the management of advanced melanoma during COVID-19

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“Amid the COVID-19 pandemic cancer patients present a unique challenge, as they are often immunosuppressed or subject to treatment-related toxicities that may cause severe disease manifestations.”

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Amid the COVID-19 pandemic cancer patients present a unique challenge, as they are often immunosuppressed or subject to treatment-related toxicities that may cause severe disease manifestations. The practical impact of the COVID-19 pandemic on the management of advanced melanoma warrants further consideration. Restrictions on the US healthcare system to mitigate COVID-19 transmission have significantly altered melanoma management practices from the initial diagnosis of primary cutaneous disease to systemic treatment for advanced and metastatic presentations. We herein report our experience and recommendations for this patient population, highlighting the importance patient-centered planning based on tumor characteristics, resource availability and the local state of COVID-19 control.

Background

COVID-19 originated in late 2019, caused by the novel coronavirus SARS-CoV2, and has since expanded to pandemic levels, causing unparalleled strain on global financial and healthcare systems. While often presenting with nonspecific symptomatology, including dyspnea, fever and cough, a wide-range of more severe presentations have been documented. These severe complications include respiratory failure, sepsis, kidney injury, vasculitis and even neurologic damage. Management has largely emphasized mitigating transmission and protecting vulnerable populations with underlying medical conditions with early evidence for modest efficacy of antiviral therapies. Cancer patients present a unique challenge, as this population is often immunosuppressed and treated with medications that carry a significant risk for toxicities that may predispose patients to severe complications. In fact, cancer patients, particularly those with pulmonary involvement, have been documented to have a higher incidence of COVID-19 infection and rate of severe disease [1,2]. With approximately 80,000 new cases of melanoma annually in the USA, the impact of COVID-19 on the management of melanoma warrants further consideration [3]. This paper aimed to synthesize our experience and recommendations for the management of patients with advanced melanoma during the COVID-19 pandemic.

Management of primary disease

Although beyond the scope of this paper, changes to the initial management of localized melanoma are also a salient concern. Since melanoma is usually first identified through routine skin exams or in response to a changing cutaneous lesion, restrictions or hesitance to attend these appointments may lead to delayed diagnosis and possibly upstaging. Telehealth initiatives and electronic solutions may provide appropriate outlets for initial melanoma screening and evaluation, although challenges remain [4]. In addition, patients with confirmed melanoma may experience delays in surgical resection and lymph node staging, if applicable. Fortunately, most surgeries for active cancer management have not been subject to stringent restrictions on elective procedures in most regions.

Management of advanced disease

Metastatic or unresectable disease, however, requires more urgent initiation of systemic therapy. Prior to making decisions on the initiation or continuation of these therapies now in the COVID-19 era, there are several factors that should be considered on an individualized, patient by patient basis. In general, these considerations include: the aggressiveness of the patient's disease; the dosing schedule and ability to receive treatment at home or outpatient facilities; the risk and toxicity profile of treatment and the state of COVID-19 in the local hospital system and availability of resources for protection and management. At this time, there is no clear evidence that immune stimulating or cytotoxic agents worsen outcomes with COVID-19 although this remains a topic of ongoing, intensive study [5].

In this patient population, treatment with immune checkpoint inhibitors (ICIs) has emerged as standard therapy. Overall, these agents have produced a 5-year overall survival rates of 40–50% [6]. Notably, these agents can precipitate immune-related adverse events (irAEs) caused by aberrant immune cell activation targeting host tissues, which often require immunosuppressive therapies and hospitalization for management. Patients that require prolonged or high-dose immunosuppressants could be at increased risk for COVID-19 transmission and severe disease, as well as iatrogenic complications from hospitalization. In addition to the risks of immunosuppressive therapy, an irAE of particular interest is pneumonitis. With the significant pulmonary involvement of COVID-19 and often severe manifestations of pneumonitis, a combination of the two presents a potentially life-threatening scenario. Other overlapping clinical presentations may occur, including hepatitis and myocarditis, which can mimic their COVID-19 induced analogs [7]. Therefore, if possible, medication selection and dosing regimens should be optimized. For example, anti-PD-1 inhibitors (nivolumab), are often combined with CTLA-4 inhibitors (ipilimumab). Although increasing the response rates and progression-free survival in patients with metastatic melanoma, the addition of ipilimumab significantly increases the risk of severe irAEs from 15–20 to 50–60% compared with anti-PD-1 monotherapy [8]. With a goal of reducing the need for immunosuppressive therapy, the risk of COVID-19 transmission from hospitalization, and the rate of potentially severe auto-inflammation, the use of ipilimumab should be thoughtfully considered. We suggest that most patients, therefore, in the absence of bulky, symptomatic disease, active brain metastases or other adverse prognostic features, preferentially receive anti-PD-1 monotherapy during this time. In addition, in the case of a patient testing positive for COVID-19 while receiving ICI, treatment should be held for at least 1 week following symptom resolution to avoid the theoretical risk of developing concurrent pneumonitis.

Another consideration while on ICI therapy is the dosing schedule. Although instituting strict screening procedures and incorporating social distancing may mitigate the risk, any contact with the healthcare system can present a possibility of COVID-19 transmission. Partly in response to the pandemic, the US FDA accelerated approval to use pembrolizumab every 6 weeks, compared with the previous standard of every 3 weeks [9]. Nivolumab may also be administered every 4 weeks. Some regions may also have options for home-care infusion, although it is not clear how often this will occur. Some patients may also consider discontinuing therapy following an extended duration (e.g., patients with a complete response following 1–2 years of therapy) or pausing therapy in areas of high COVID-19 prevalence.

Targeted therapy with BRAF and MEK inhibitors also may be an option for patients with metastatic melanoma harboring BRAF V600 mutations. Currently, there is no evidence that BRAF and MEK inhibitors either hinder the antiviral immune response or exacerbate harmful inflammation if an infection occurs. Thus, one could consider using BRAF/MEK inhibition when indicated without obvious restrictions during the COVID-19 pandemic.

After metastatic disease is controlled, there are aspects to consider with further management. In the case of isolated areas of metastatic disease, surgical resection and radiotherapy may be effective options. A few considerations include the risk and benefit of delaying therapy, the ICU capacity if surgical treatment requires prolonged postoperative observation and the availability of protected rooms and equipment for the patient.

Conclusion

The COVID-19 pandemic has placed extreme strain on the USA healthcare system and caused significant protocol changes to care for patients with melanoma. From initial screening to treatment of metastatic disease, practices have changed to restrict contact with the healthcare system and ensure proper protective measures are in place to limit transmission to this vulnerable patient population. Overall, these changes highlight the importance of creating an individualized plan for the patient based on tumor characteristics, resource availability and the local state of COVID-19 control.

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