COMMENTARY

Metastatic melanoma treatment with checkpoint inhibitors in the COVID-19 era: experience from an Italian Skin Cancer Unit

Melanoma epidemiology has shown a constant increase in the last few decades even if mortality is low[1] and only a small percentage of patients develop metastatic disease.[2] For these patients, immunotherapy with checkpoint inhibitors (ICI) significantly improves disease outcome with a median survival more than 2 years.[3] The same drugs are used as adjuvant treatment in disease-free patients.[4]

Coronavirus disease-19 (COVID-19) is now a pandemic disease with lung manifestations, which can bring severe acute respiratory distress. The most important risk factors related to a higher death risk for COVID-19 pneumonia are elderly age and comorbidities (hypertension, diabetes, previous cancer).[5] In Italy today, the number of total positive cases is 175 025 with 23 227 deaths.[6] Our University Hospital is located in Piedmont (North-Western Italy, near to Lombardy) where >15 000 cases have been observed at 4.2% actual daily increase.

Cutaneous manifestation of COVID-19 has been reported;[7] however, no data are available in literature about the impact COVID-19 infection has on ICI treatment in metastatic melanoma patients also considering the low melanoma incidence in China where COVID-19 pandemic started. Literature data report only one advanced metastatic lung cancer patient who developed COVID-19 infection during ICI with a rapid fatal evolution.[8] No guidelines on management of ICI-treated metastatic melanoma patients are available, even if some interesting points can be underlined. ICI could protect from infection as its immune mechanism[9] is similar to those involved in the immune response against viral infections (interferon and Th1/Th17 up-regulation).[10] On the opposite, the severity of COVID-19 manifestations has been associated with increased production of pro-inflammatory cytokines as IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNFα.[5] This could explain the rapid fatal outcome of the patient described by Bonomi *et al.*[8] Other considerations are represented by the fact that systemic steroids used for the treatment of ICI adverse events could hamper the immune response against the virus; similarly, the differential diagnosis between viral pneumonia and lung toxicity to ICI could be difficult due to the similar interstitial pattern.[2,3]

At the beginning of March, 80 metastatic melanoma patients were under ICI in our centre (62 nivolumab and 18 pembrolizumab), the majority with advanced metastatic disease (49; 61%), whilst 31 in adjuvant treatment for disease-free stage III-IV. The issues addressed in this paper are whether ICI treatment should be delayed, withdrawn or started in the case of new treatment.

A strict procedure was put in place at hospital entrance: all the patients were screened by a nurse team about symptoms, contact with symptomatic or COVID-positive patients, presence of symptomatic or COVID-positive people in the family, and then checked for temperature before admittance. Patients allowed to enter, were invited to carefully disinfect their hands and given rubber gloves and surgical masks. In the onco-dermatological service, each patient was put in separate places with adequate distance and no accompanying people.

Our decision in the first weeks of COVID-19 outbreaks was to offer all the patients the possibility to continue treatment but to suggest elderly patients with comorbidities and low tumour burden, as well as patients in adjuvant treatment, to postpone treatment. To support this management, literature data show similar outcomes in patients who discontinued nivolumab plus ipilimumab because of adverse events with respect to those who continued.[11] Moreover, the KeyNote-006 study showed that, at 2-year follow-up, 78% of patients who completed 2 years of pembrolizumab achieving complete/partial response or stable disease[12] maintain the response. All patients were called to inform them about the situation, contagious risk and possibilities of continuing or interrupting the treatment.

A total of 57 (71%) patients continued treatment without interruptions, whilst 16 postponed their therapy of 1 (14 patients; 17.5%) or 2 cycles (two patients; 2.5%). The remaining 7 (9%) suspended treatment due to progression (5), completion of schedule (1) or were lost to follow-up (one patient). The duration of interruption ranged from 1 week to 2 months. Patients who interrupted treatment were elderly (median 78 years; eight patients having >80 years), with comorbidities (10/16). Six were in adjuvant treatment and 10 had metastatic disease, all of whom in response (five complete and on partial) or stable disease. During the COVID-19 pandemic, moreover, four patients started a new treatment.

A second different modality of treatment management was developed since April, advising patients to re-start treatment because COVID-19 pandemic is still continuing and the duration of the critical situation is unknown. Therapy was then resumed in 10/16 patients (62.5%) previously delayed. At the time of writing, no patients under ICI developed COVID-19 infection.

In conclusion, our experience supports the possibility of continuing ICI in metastatic melanoma patients even if evaluating on a patient basis (elderly, comorbidities, ongoing response, adjuvant treatment), the possibility of delaying the subsequent course. Careful patient management is warranted in the hospital and strict monitoring of symptoms in case of suspicion.

Conflict of interest

Paolo Fava, Matteo Brizio, Elena Marra, Marco Rubatto, Andrea Agostini, Luca Tonella, Simone Ribero and Maria Teresa Fierro have nothing to disclose. Pietro Quaglino is on the advisory board of Novartis, BMS, MSD and Pierre Fabre and received fees for lectures from Novartis, BMS, MSD and Pierre Fabre.

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