Leukemia Research Reports 14 (2020) 100212

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Management of multiple myeloma during COVID-19 pandemic

YS Jethava[a,*], Rafael Fonseca[b], Ola Landgren[c]

[a] Division of Hematology and Cellular Therapy, University of Iowa Hospitals and Clinics, 200 Hawkins Dr, 5970 JPP, Iowa City, IA 52242, United States
[b] Interim Executive Director, Mayo Clinic Comprehensive Cancer Center, Director for Innovation and Transformational Relationships, Getz Family Professor of Cancer, Distinguished Mayo Investigator, 5777 East Mayo Boulevard, Phoenix, AZ 85054, United States
[c] Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, United States

A B S T R A C T

At the end of 2019, a novel coronavirus was identified as the cause of pneumonia cases in Wuhan, a city in the Hubei Province of China. On January 30, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a public health emergency of international concern and, in March 2020, began to characterize it as a pandemic. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019.

Multiple Myeloma (MM) affects over 32,000 Americans annually [1]. More than 130,000 people are living with the disease, making MM the most common blood cancer in the U.S. population [2]. In this review, we will discuss issues related to COVID-19 infection and its implications for the MM patient population.

COVID-19 background

Disease

The incubation period for COVID-19 is as long as 14 days following exposure, but most cases occur approximately four to five days after exposure. In a study of 1099 patients with confirmed symptomatic COVID-19, the median incubation period was four days [3–5]. The spectrum of symptomatic infection ranges from mild to critical; however, most infections are not severe [5–7]. In a report from the Chinese Center for Disease Control and Prevention, which included approximately 44,500 confirmed COVID 19 infections [8], mild was reported in 81 percent, the severe disease was reported in 14 percent, and critical disease was reported in 5 percent. The overall case-fatality rate (CFR), that is death probability among those diagnosed, in this study was 2.3 percent. In non-critical cases, there were no reported deaths. The CFR for COVID-19 is not well known, but ranges between 1-3% in most published studies. The severity of illness depends on demographic and laboratory factors.

Table 1 illustrates the demographic factors related with the severity of illness [4,9].

Patients with severe COVID-19 can evolve into a clinical syndrome similar to what is observed with the cytokine release syndrome; persistent fevers, elevated inflammatory markers (eg, D-dimer, ferritin), and elevated pro-inflammatory cytokines [11,12]. High D-dimer levels and more severe lymphopenia have been associated with mortality [13]. Laboratory features associated with worse outcomes listed in Table 2 [14–16].

The patients with COVID-19 infection have unique findings on computed tomography (CT).

In the United States, the CDC recommends the collection of a nasopharyngeal swab specimen to test for SARS-CoV-2 [38]. While expectorated sputum can also be tested, particularly if bronchoscopy is performed, induction of sputum is not recommended because of the risk to create aerosols. SARS-CoV-2 RNA is detected by reverse-transcription polymerase chain reaction (RT-PCR) [22]. There can be false-negative tests from upper respiratory specimens, and if initial testing is negative, but there is a strong suspicion, the test should be repeated [39]. For safety reasons, viral culture is not routinely done in the clinic from specimens from a patient with suspected or documented COVID-19.

Pathophysiology and clinical course

The data so far available seem to indicate that in some circumstances the viral infection is capable of producing an excessive immune reaction, similar to 'cytokine storm' in the host leading to ARDS, while most individuals can clear the infection as other respiratory infections. The effect is extensive tissue damage due to excess of interleukin 6 (IL-6). The course of COVID-19 varies in different patients. The symptomatic infection can range from mild to critical. The median time to dyspnea is 5 to 8 days [23,7]. Acute respiratory distress syndrome (ARDS) is a significant complication in patients with severe disease and

* Corresponding author.
E-mail addresses: yogesh-jethava@uiowa.edu (Y. Jethava), fonseca.rafael@mayo.edu (R. Fonseca), landgrec@mskcc.org (O. Landgren).

https://doi.org/10.1016/j.lrr.2020.100212

Available online 13 June 2020

Table 1
Demographic factors related with severity.

- Age: Adverse impact of age
  - ○ Hospitalization rates: 20 to 29 years old- 1%, 50 to 59 years old- 4%, >80 years- 18% [8].
  - ○ Case fatality rate: 70 to 79 years – 8% and > 80 years – 15% [8, 9].
  - ○ The United States data of 2449 COVID-19 positive hospitalize patients showed that patients above 65 years of age had highest mortality [10].
- Cardiovascular disease
- Diabetes mellitus
- Hypertension
- Chronic lung disease
- Cancer
- Chronic kidney disease
- Immunocompromised conditions
- Severe obesity (body mass index ≥40
- Liver disease
- Males have comprised a disproportionately high number of deaths in cohorts from China and Italy

Table 2
laboratory findings associated with poor outcomes:

- Lymphopenia
- Elevated liver enzymes
- Elevated lactate dehydrogenase (LDH)
- Elevated inflammatory markers (eg, C-reactive protein [CRP], ferritin)
- Elevated D-dimer (>1 mcg/mL)
- Elevated prothrombin time (PT)
- Elevated troponin
- Elevated creatine phosphokinase (CPK)
- Acute kidney injury
- Higher viral RNA levels in respiratory specimens are reported in patients with severe disease [17]

can manifest shortly after the onset of dyspnea. ARDS developed in 20 percent a median of 8 days after the onset of symptoms; 12.3 percent of patients needed mechanical ventilation [11]. Other complications have included arrhythmias, acute cardiac injury, and shock. In a series of 21 critically ill patients admitted to the ICU in the United States, one-third developed cardiomyopathy [24]. According to the WHO, recovery time appears to be around two weeks for mild infections and 3 to 6 weeks for the severe disease [37].

What we know about cancer and COVID-19

Currently, there is only limited information available in cancer patients with COVID-19 infection. Available information is based on Chinese and Italian data. In a report from Italy, 20 percent of the deaths from COVID-19 in the entire country were in patients with active cancer [9]. In a small series of 28 patients with COVID-19 from Wuhan, China, the median age was 65 years, 17 percent were male and most frequent cancer type was lung cancer (25 percent) [25]. There were more severe events among the seven patients who had received chemotherapy, radiotherapy, targeted therapy, or immunotherapy within the last 14 days. Important factor is; chemotherapy within preceding 2 weeks of COVID-19 infection is an adverse prognostic factor.

Myeloma and COVID 19

At present, there is only sparse data on MM patients affected with COVID-19. Similar to the management of other malignancies, there is no "one size fits all" approach to delivering MM care during the COVID-19 pandemic. The consideration should be given to conceptual approach of the decision making in MM patients during COVID-19 pandemic, which will help in balancing the risk of progression with the delay of cancer care versus the risk for significant morbidity from COVID-19 [26].

A. Screening for COVID 19 prior to starting therapy:

It is important to ask direct questions about COVID-19 symptoms and masks should be provided to these MM patients presenting to clinic. There should be a low threshold for COVID-19 testing in these patients. We recommend COVID-19 screening for all patients with newly diagnosed MM prior to initiating induction therapy. The important thing to acknowledge is that, absence of symptoms is not associated with a predictably low viral load. If the patient tests positive for COVID-19, the CDC recommends that all treatment should be held until symptoms from COVID-19 have resolved for at least 72 h, irrespective of a cancer diagnosis [38].

B. Newly diagnosed standard risk and high-risk MM patients:

Presentation of MM can be dramatic, with the onset of hypercalcemia (28 percent), elevated creatinine (48 percent), or symptomatic spinal cord compression [27]. There is no evidence that COVID-19 infection interferes with or has an effect on the diagnosis and staging of MM. For standard risk patients, it would be reasonable to switch to weekly velcade dosing. Similarly, for young, fit patients and relapsed MM patients, carfilzomib can be switched to weekly dose. In young and fit patients, weekly carfilzomib regimen has proved to be effective [28]. Ixazomib, revlimid and dexamethasone is well tolerated, does not require infusion center visits and is very effective in newly diagnosed MM patients [29]. For regimens containing Daratumumab, only modification that can be considered is; to switch sooner to monthly daratumumab infusions than the label states. It's designed to limit the number of infusions and visits, which is reasonable during the COVID-19 outbreak.

C. Autologous stem cell transplant (ASCT):

ASCT places immunocompromised patients at a higher risk of infections, especially during outbreaks. Patients encounter long term sustained immunosuppression and the need for 1year re-vaccinations after ASCT. While several organizations have recommended delaying ASCT, there is no universally accepted practice. The American Society of Hematology (ASH) recommends delaying the stem cell transplant (including hematopoietic stem/progenitor cells collection and storage) until the pandemic abates. The International Myeloma Society recommends that frontline ASCT should be postponed, if possible. Patients should be tested for COVID-19 before undergoing ASCT whenever possible.

Given that it is unknown whether there could be additional seasonal outbreaks in upcoming winter of 2020 as well as following years, it is good clinical practice to have this discussion with every patient – given that ASCT causes an extended window of significant immunosuppression. Current re-immunization programs for melphalan-induced inactivation of prior vaccines recommend that vaccination (including: pertussis, diphtheria, tetanus, Hemophilus influenzae, pneumococcal, and hepatitis A and B) begin 12 months after ASCT [30]. When a vaccine becomes available towards SARS-CoV-2, it has to be added to these re-immunization programs. We recommend testing for COVID-19, 72 h prior to hematopoietic stem/progenitor cells collection and prior to starting conditioning.

D. Relapse/refractory MM patients:

It is imperative for clinicians to have proactive discussions with patients about goals of care and advance care planning, especially for those with relapsed/ refractory MM during COVID-19 pandemic. In these patients, individualized decisions should be taken and the treatment should be continued. If the patient has stable disease or is in very good partial remission (VGPR), time between infusions can be extended. For example, if patient is on Daratumumab based regimen for

Table 3
Imaging findings associated with COVID 19 [18–21].

CT images **more** likely with COVID 19 infection	CT images **less** likely with COVID 19 infection
Peripheral distribution, ground-glass opacities, fine reticular opacities, vascular thickening, reverse halo sign	Central and peripheral distribution, air bronchogram, pleural thickening, pleural effusion, lymphadenopathy

Table 4
Possible considerations during COVID-19.

Newly Diagnosed MM:
- Weekly velcade dosing for standard risk patients
- Weekly Carfilzomib dosing regimens for young/fit patients or high-risk patients
- Oral regimen; Ixazomib/Revlimid/Dex

Elderly patients:
- Consider changing velcade dosing to weekly schedule
- Oral regimen; Ixazomib, revlimid and dexamethasone
- Consider going to monthly daratumumab earlier than recommended

Lymphopenia is unfavorable in active COVID-19 infection, hence consider lowering the dose of dexamethasone

relapsed MM and has achieved VGPR, then Daratumumab infusions can be switched to monthly schedule, sooner than indicated. Other modifications such as; once weekly dosing schedules, exploring home chemotherapy infusions, minimizing blood draws, engaging with home health services for blood draws, minimizing imaging studies and bone marrows must be considered on individualized case by case basis. Often, high dose chemotherapy, salvage ASCT, CAR-T cells or bispecific antibodies (BiTE) trial is the only remaining option for relapsed/refractory MM patient population. In the patients on immune check-point inhibitor therapy trials, treatment-related pneumonitis is a concern, which may increase the risk of severe complications if the patient develops concurrent COVID-19 infection. Hence immune check-point inhibitor therapy trials can be withheld. It is important to minimize time in waiting rooms, rearranging patient contact areas to maximize social distancing, face masks and frequent hand washing should be implemented.

Table 4 illustrates possible therapeutic regimens for COVID-19 MM patients.

E. MGUS and SMM patients:

The routine follow-up of smoldering myeloma (SMM) or monoclonal gammopathy of undetermined significance (MGUS) patients can be delayed. MGUS patients have approximately 2-fold increased risk of viral infections, such as influenza and herpes zoster [31]. Depressed antibody titers to a number of common infectious pathogens have been found in several conditions associated with presence of an M-protein [32]. Hence it is imperative that in MGUS and SMM patients with fever and respiratory symptoms, COVID-19 is ruled out. Although data regarding COVID-19 in MGUS and SMM patients is not available, there is a theoretical possibility that a delayed immune reconstitution results in shedding virus for longer period of time. If true, this can put immediate family members and healthcare workers at higher risk.

Supportive care and treatment

There is presently no vaccine or specific anti-viral drug regime for the critically ill patients. The management of patients mainly focuses on the provision of supportive care, e.g., oxygenation, ventilation, and fluid management. Combination treatment of low-dose systematic corticosteroids and anti-viral and atomization inhalation of interferon have been encouraged as part of critical COVID-19 management. In the published reports from China, more than 85% of patients received antiviral agents, including oseltamivir, ganciclovir and lopinavir/ritonavir tablet [33]. Remdesivir is currently under trials at more than ten medical institutions in Wuhan. An old anti-malarial, chloroquine phosphate, has been effective in inhibiting the exacerbation of pneumonia due to its anti-viral and anti-inflammatory activities [34]. There is a case report of one MM patient with COVID-19 infection empirically treated with tocilizumab for a clinical picture of ARDS. The symptoms are driven by excessive pro-inflammatory milieu and hence anti-IL6 strategy might be worth exploring [35]. A recent study of compassionate use remdesivir has shown positive outcome and will hopefully be approved for the treatment [36]. Ultimately, it is combination of social distancing, improved hygienic practices, and universal masking, which will be key in controlling COVID-19 spread (Table 3).

Minimizing the compromise of social distancing during myeloma care

Patients undergoing cancer care counseling, active treatment, surveillance are highly exposed and there is a large number of potential opportunities for viral transmission for both patients and caregivers. Personal contact is often important for providing confidence, reassurance and comfort to the patient. While telemedicine can be utilized in an effort to maximize social distancing, it has the potential to interrupt important aspects of the patient's relationships with the care team. This can lead to miscommunication and misunderstandings as well as avoidable delays and even adverse events related to improper care. As patients and providers jump headfirst into utilizing video platforms to communicate and deliver care, both must accept the benefits as well as the risks.

Declaration of Competing Interest

Dr Yogesh S Jethava: none.
Dr Rafael Fonseca: none.
Dr. Landgren reports grants from NIH, FDA, MMRF, IMF, LLS, Perelman Family Foundation, Rising Tide Foundation, Janssen, Takeda, Glenmark, Seattle Genetics, Karyopharm; personal fees from Adaptive Biotech, Binding Site, BMS, Cellectis, Juno, and Pfizer; and IDMC from Takeda, Merck, and Janssen."

References

[1] Siegel, R.L., Miller K.D., Jemal, A., *Cancer statistics, 2020*. (1542-4863(Electronic)).
[2] Kyle, R.A., et al., *Incidence of multiple myeloma in Olmsted County, Minnesota: trend over 6 decades*. (0008-543X (Print)).
[3] Li, Q., et al., *Early Transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia.* (1533-4406(Electronic)).
[4] Guan, W.A.-O.X., et al., *Clinical characteristics of coronavirus disease 2019 in China*. LID -10.1056/NEJMoa2002032 [doi]. (1533-4406(Electronic)).
[5] Chan, J.F., et al., *A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster*. (1474-547X (Electronic)).
[6] Bajema Kl Fau - Oster, A.M., et al., *Persons evaluated for 2019 novel coronavirus - United States, January 2020*. (1545-861X (Electronic)).
[7] Huang, C., et al., *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China*. (1474-547X (Electronic)).
[8] Wu, Z. and J.M. McGoogan, *Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention*. LID -10.1001/jama.2020.2648 [doi] FAU - Wu, Zunyou. (1538-3598(Electronic)).
[9] Onder, G., G. Rezza, and S. Brusaferro, *Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy*. LID -10.1001/jama.2020.4683[doi] FAU - Onder, Graziano. (1538-3598(Electronic)).
[10] *Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020*. (1545-861X (Electronic)).
[11] M. Affer, et al., Promiscuous MYC locus rearrangements hijack enhancers but mostly super-enhancers to dysregulate MYC expression in multiple myeloma,

Leukemia 28 (8) (2014) 1725.
[12] Mehta, P., et al., *COVID-19: consider cytokine storm syndromes and immunosuppression*. (1474-547X (Electronic)).
[13] Chen, N., et al., *Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study*. (1474-547X (Electronic)).
[14] Zhou, F., et al., *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.*(1474-547X (Electronic)).
[15] Wu, C., et al., *Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China*. LID -10.1001/jamainternmed.2020.0994 [doi]. (2168-6114(Electronic)).
[16] Shi, S., et al., *Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China*. LID -10.1001/jamacardio.2020.0950 [doi]. (2380-6591(Electronic)).
[17] Liu, Y., et al., *Viral dynamics in mild and severe cases of COVID-19*. LID -S1473-3099(20)30232-2[pii] LID -10.1016/S1473-3099(20)30232-2 [doi] FAU - Liu, Yang. (1474-4457(Electronic)).
[18] Wong, H.Y.F.A.-O.h.o.o., et al., *Frequency and distribution of chest radiographic findings in COVID-19 positive patients*. (1527-1315(Electronic)).
[19] Shi, H., et al., *Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study*. (1474-4457(Electronic)).
[20] Zhao, W., et al., *Relation between chest ct findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study*. (1546-3141(Electronic)).
[21] Bai, H.X., et al., *Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT*. (1527-1315(Electronic)).
[22] Patel, A. and D.B. Jernigan, *Initial public health response and interim clinical guidance for the 2019 novel coronavirus outbreak - United States, December 31, 2019-February 4, 2020*. (1545-861X (Electronic)).
[23] Wang, D., et al., *Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China*. LID -10.1001/jama.2020.1585 [doi]. (1538-3598(Electronic)).
[24] Arentz, M., et al., *Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State*. LID -10.1001/jama.2020.4326 [doi] FAU - Arentz, Matt. (1538-3598(Electronic)).
[25] Zhang, L., et al., *Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China*. LID -S0923-7534(20)36383-3[pii] LID -10.1016/j.annonc.2020.03.296 [doi]. (1569-8041(Electronic)).
[26] Kutikov, A., et al., *A War on two fronts: cancer care in the time of COVID-19*. LID -10.7326/M20-1133 [doi] FAU - Kutikov, Alexander. (1539-3704(Electronic)).
[27] Kyle, R.A., et al., *Review of 1027 patients with newly diagnosed multiple myeloma*. (0025-6196(Print)).
[28] Moreau, P., et al., *Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study*. (1474-5488(Electronic)).
[29] S.K. Kumar, et al., Ixazomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma: long-term follow-up including ixazomib maintenance, Leukemia 33 (7) (2019) 1736–1746.
[30] Tomblyn, M., et al., *Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective*. (1523-6536(Electronic)).
[31] S.Y. Kristinsson, et al., Monoclonal gammopathy of undetermined significance and risk of infections: a population-based study, Haematologica 97 (6) (2012) 854–858.
[32] J. Karlsson, et al., Comparative study of immune status to infectious agents in elderly patients with multiple myeloma, Waldenstrom's macroglobulinemia, and monoclonal gammopathy of undetermined significance, Clin Vaccine Immunol 18 (6) (2011) 969–977.
[33] Lai, C.C., et al., *Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges*. (1872-7913(Electronic)).
[34] Gao, J., Z. Tian, and X. Yang, *Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies*. (1881-7823(Electronic)).
[35] Zhang, X., et al., *First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab*. (2473-9537(Electronic)).
[36] J. Grein, et al., Compassionate use of remdesivir for patients with severe Covid-19, New Eng J Med (2020).
[37] World Health Organization Director-General's opening remarks at the media briefing on COVID-19 - February 24 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19–24-february-2020(Accessed on February 26, 2020).
[38] Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons under investigation (PUIs) for coronavirus disease 2019 (COVID-19). February 14, 2020. https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html (Accessed on March 15, 2020).
[39] World Health Organization. Coronavirus disease (COVID-19) technical guidance: Surveillance and case definitions. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/surveillance-and-case-definitions (Accessed on February 28, 2020).