IN THE SPOTLIGHT

Don’t Compromise Myeloma Care Due to COVID-19 Pandemic!

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Summary: Patients with active myeloma, especially with earlier stages of the disease, are susceptible to COVID-19 infection and can have adverse outcomes, even in those on first-line treatment. Importantly, myeloma therapy can be safely administered, and optimal control of myeloma is associated with improved outcome.

See related article by Hultcrantz et al., p. 234 (1).

In this issue of Blood Cancer Discovery, Hultcrantz and colleagues report on the clinical features and outcomes of 100 patients with multiple myeloma and COVID-19 infection at five academic centers in New York City, which was the epicenter of the infection in the United States (1). They describe a higher incidence of adverse outcomes in Hispanic/Latinos and African Americans, as well as in patients with higher levels of inflammatory markers and cytokines. Moreover, 29% of hospitalized patients died, highlighting the severity of COVID-19 infection in these patients.

A recent report of COVID-19 infection in 890 patients with cancer in Europe (the European cancer cohort) demonstrating an increased mortality in patients with hematologic malignancies than breast cancer and other solid tumors (2), coupled with other reports documenting inpatient mortality rates of COVID-19 infection in patients with myeloma ranging from 27% to 55%, further highlights the significance of COVID-19 infection in these patients (3, 4).

An important aspect of COVID-19 infection is the relationship between age and patient outcome. Infection has been reported in a broad age range both in the general population and specifically in patients with cancer, suggesting that age by itself does not significantly affect susceptibility (5). For example, in the VA cohort study with 1,794 patients with cancer with COVID-19 positivity from the U.S. Veteran Affairs database, the prevalence of COVID-19 was similar across all ages (6). Of note, however, higher numbers of older patients with cancer may be diagnosed, as they are tested for COVID-19 more frequently. In the same study, COVID-19-related mortality was strongly associated with age, ranging from 0.23% in patients less than 50 years old to 20.5% in patients older than 80 years ($P < 0.001$). Although the New York City (NYC) report did not identify age greater than 65 years to be an independent risk factor associated with adverse outcome (1), a larger study of 650 patients with myeloma with COVID-19 infection from the International Myeloma Society (the IMS cohort) did find a relationship between age and mortality, with an estimated probability of death of 17.8%, 31.4%, and 49.3% in patients aged 40, 60, and 80 years, respectively (4). This and other studies in myeloma demonstrate a clear relationship between increasing age and adverse outcome of COVID-19 infection, particularly important since the median age of newly diagnosed patients with myeloma is 71 years.

In the VA cohort, the prevalence of COVID-19 infection in patients with cancer was 15% and 10.9% in African American and Hispanic/Latino patients, respectively, compared with 5.5% in whites (6). Importantly, the rate of hospitalization was 3.5-fold higher in African Americans, but the COVID-19-related mortality was similar between the two populations. Myeloma is more common in African Americans, but the NYC study cannot address the relative incidence of COVID-19 in racial populations; it did demonstrate a higher risk of adverse outcome in African American and Latino populations. Although the development of novel therapies over the last 10 to 15 years has transformed the treatment paradigm in myeloma, the median survival in African Americans has not been prolonged to the same extent as in other patient subgroups. Moreover, a recent AACR FDA Workshop demonstrated low rates of enrollment of African Americans on myeloma clinical trials; however, African American patients treated with novel agents have outcomes similar and even superior to other patient subgroups (7). Whether adverse outcome of COVID-19 infection in African Americans is due to unique susceptibilities, genetic or environmental factors, lack of access to current myeloma therapies, and/or access to intensive and supportive care, including antiviral therapy and ventilatory support for COVID-19 infection, remains unclear. The CCC19 study of 2,186 U.S. adults with invasive cancer and COVID-19 infection did find that African American patients were approximately half as likely to receive remdesivir as white patients (8). Importantly, the COVID-19 pandemic has further emphasized disparity in access to health care for patients with cancer and/or COVID-19 infection worldwide.

The adverse outcome of COVID-19 infection has been associated with comorbidities in most studies, including...
in patients with cancer and myeloma; however, the types of comorbidities have been variable. For example, in the European cancer cohort study, COVID-19 with cognitive impairment and chronic kidney disease was associated with higher mortality rates (2). The CCC19 study found that individual comorbidities were not statistically significant (8), but that the Charlson Score representing general performance status and other comorbidities was correlated with increased COVID-19–attributable deaths, ranging from 3.1% in patients with Charlson score 0 to 15.0% in patients with Charlson score $\geq 5$ ($P < 0.001$; ref. 6). A Spanish cohort study found that at least one comorbidity was associated with COVID-19 infection in 75% patients with myeloma, as well as in 77% age- and sex-matched noncancer patients (9). In the IMS cohort, multivariate analysis identified renal disease as an independent predictor of adverse outcome (4). In contrast to these studies, comorbidities including hypertension and diabetes in patients with myeloma were not associated with adverse outcome of COVID-19 infection in the NYC cohort.

The impact of cancer treatment in patients with COVID-19 is variable depending on both type of cancer and therapy being administered, including its impact on immune and inflammatory response. For example, within the VA cohort, provision of chemotherapy, targeted therapy, and immunotherapy as well as cancer therapy within 6 months of the COVID-19 infection was not associated with increased mortality (6). Similarly, the European cancer cohort confirmed that the type of systemic anticancer therapy was not associated with COVID-19 severity, and, in fact, active anticancer therapy at the time of COVID-19 was associated with lower risk of complicated disease (2). Several reports of myeloma and COVID-19 infection highlight the importance of not compromising the use of novel therapies for myeloma, including high-dose therapy and autologous stem cell transplantation, due to COVID-19 infection. For example, high-dose therapy and stem cell transplant within 1 year of COVID-19 infection did not portend adverse patient outcome in the NYC cohort or the IMS cohort. Most importantly, several reports highlight the need to achieve disease control in myeloma and not to compromise primary therapy due to COVID-19 infection. For example, suboptimal myeloma disease control was associated with adverse outcome in the IMS report (4). Access to intensive care unit and ventilatory support varies in the reports of patients with myeloma with COVID-19 infection and clearly impacts outcome.

Within patients with myeloma infected with COVID-19, does immune status impact outcome? Defects in adaptive and innate immunity, including both cellular and immune responses, are a hallmark of myeloma. Patients with myeloma are therefore more susceptible to infections and are treated with intravenous immunoglobulin in the context of repeated life-threatening infections. Paradoxically, the extent of immunoparesis may not correlate with outcome of COVID-19 infection in patients with myeloma. Patients with newly diagnosed myeloma on induction therapy, and even patients with monoclonal gammapathy of undetermined significance or smoldering multiple myeloma not requiring therapy, are included in the NYC cohort and other reports of COVID-19 infection. Clearly, these patients have not developed progressive immunosuppression due to progressive disease and attendant to therapy. Indeed, IgG $<650$ mg/dL was not associated with adverse outcome in the NYC cohort; rather, higher levels of inflammatory markers and cytokine activation portended inferior outcome in these patients. In the IMS cohort, a higher susceptibility to COVID-19 was observed in earlier stages of myeloma, since 36% of the patients with COVID-19 infection were diagnosed with myeloma in 2019 to 2020 compared with 22% patients overall diagnosed with myeloma in this timeframe, per Surveillance, Epidemiology, and End Results data (4). It is interesting to speculate that preserved immune competence in patients with myeloma allows for the development of cytokine storm and pulmonary toxicity/acute respiratory distress syndrome and poor outcome.

This experience is based on “real-world” evidence rather than prospective clinical observational trials. Nonetheless, the aggregate experience to date suggests that patients with myeloma are likely more susceptible to COVID-19 infection and can have adverse outcomes, even in those on first-line treatment or not requiring therapy. This highlights the need for heightened precautions including handwashing, wearing a mask, social distancing, and avoiding viral exposure in all patients with these plasma cell disorders and their families. Importantly, the emerging data suggest that myeloma therapy can be safely administered in patients with COVID-19 infection, and that myeloma disease control portends improved outcome of COVID-19 infection.

Disclosure of Potential Conflicts of Interest

N.C. Munshi reports personal fees from Bristol-Myers Squibb (consultant), Janssen (consultant), Amgen (consultant), Takeda (consultant), Abbvie (consultant), and other from OncoPep (scientific founder) outside the submitted work. K.C. Anderson is a consultant/advisor for Bristol-Myers Squibb, Janssen, Amgen, Takeda, Sanofi, Gilead, and Precision Biosciences and Scientific Founder of OncoPep and C4 Therapeutics.

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