ORIGINAL ARTICLE

Outcome of COVID-19 infection in 50 multiple myeloma patients treated with novel drugs: single-center experience

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Abstract

Infections are the primary cause of morbidity and mortality in multiple myeloma (MM) patients (pts). The aim of our retrospective analysis was to evaluate incidence and course of COVID-19 infection in a cohort of 351 MM outpatients treated with novel drugs. COVID-19 disease was detected in 50/351 pts (14%); median age was 68 years. Gender, ISS stage, and last treatment lines were as follows: male 32, female 18; ISS-I 19, ISS-II 20, ISS-III 11; daratumumab-based 15, lenalidomide-based 12, bortezomib-based 17, other 6. Positive PCR test at COVID-19 diagnosis was present in all pts; anti-myeloma treatment was interrupted. Hospitalizations for COVID-19 pneumonia were necessary for 28/50 pts (56%), 18/50 pts (36%) in standard unit (SU) 10/50 pts (20%) in intensive care unit (ICU), and 9/50 pts (18%) died. The statistically significant parameters for COVID-19 hospitalization were as follows: responsive versus non-responsive disease ($p = 0.027$), ECOG performance status 0–2 versus ≥ 3 ($p = 0.014$), presence of comorbidities (0–1 versus ≥ 2, $p = 0.043$). The statistically significant factors for COVID-19 death were as follows: ECOG 0–2 versus ≥ 3 ($p = 0.001$), presence of comorbidities (0–1 versus ≥ 2, $p = 0.007$), serious course of COVID-19 disease with ICU hospitalization (SU versus ICU, $p = 0.001$). None of the other studied risk factors was associated with poor outcome (age, gender, ISS stage, immunoparesis, type of anti-myeloma treatment). Full recovery from COVID-19 infection was observed in 41/50 pts (82%) in median of 32 days. The course of COVID-19 disease in MM pts was mostly moderate or serious with 56% of hospitalizations and 18% of deaths.

Keywords Multiple myeloma · COVID-19 · Novel drugs · Hospitalization · Mortality

Introduction

The coronavirus disease 2019 (COVID-19), caused by the coronavirus SARS-Cov-2, has become a global pandemic since its first occurrence in late 2019 [1]. Clinical manifestation of COVID 19 is very variable, from patients (pts) with mild, mostly respiratory symptoms to pts with severe COVID pneumonia and multi-organ failure [2]. Reported risk factors for severe COVID-19 disease are predominantly advanced age and various comorbidities [3]. Cancer patients are at higher risk of developing a severe form of COVID-19 [4].

Optimal treatment for COVID 19 is not yet clear; various treatment options have been published with different results. Currently, there is no standard approved therapy for COVID-19; mostly supportive care has been often used for COVID-19 pts [5]. Some studies reported remdesivir as well as treatment with convalescent plasma as beneficial treatment possibilities for pts hospitalized for COVID-19 [6, 7].

Multiple myeloma (MM) is a hematological malignancy involving plasma cells; MM pts have an inherently compromised humoral and cellular immunity [8, 9]. Pathogenesis of MM results in the suppression of the adaptive immune system and leads to low levels of immunoglobulin production. Immunoparesis (hypogammaglobulinemia) is very frequent; it is present in 85–90% of MM pts [10, 11]. Correlation of immunoparesis and increased risk of adverse COVID-19 outcome is unclear.

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The introduction of new therapeutic agents, such as immunomodulatory drugs (IMIDs), proteasome inhibitors (PI), and monoclonal antibodies, has resulted in significant progress in the treatment of MM with increased survival rates [12]. However, several of these novel treatments in combination with corticosteroids are associated with an increased risk of infections with substantial hematological toxicity, including neutropenia and lymphopenia [13–15].

The aims of our retrospective analysis were to evaluate incidence and course of COVID-19 infection and clinical outcome in a cohort of 351 MM pts treated with novel drugs in one institution and to define the possible significant laboratory and clinical prognostic parameters for adverse outcome of COVID-19-associated pneumonia, necessity of hospital admission for COVID-19 or death for COVID-19 in these immunocompromised MM pts.

Patients and methods

Incidence of COVID-19 disease and immunoparesis in 351 MM patients treated with novel drugs

From October 2020 to February 2021, 351 (100%) symptomatic MM pts were treated at the outpatient clinic of the Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Czech Republic, with various combinations of novel drugs. All patients signed the informed consent form approved by the Ethics board of the hospital before start of MM treatment. COVID-19 infection was detected in 50/351 pts (14%); all these pts were SARS-Cov-2 positive as confirmed by either PCR test or antigen test from a nasopharyngeal swab. All patients with suspected COVID-19 pneumonia received computer tomography (CT) examination of thorax. Immunoparesis (reduction below the lower normal limit of one or two uninvolved immunoglobulins—IgG ˂ 6.7 g/L, IgA ˂ 0.88 g/L, IgM ˂ 0.27 g/L) was presented in 85% (298/351) of pts at the start of anti-myeloma treatment. There were no significant differences in incidence of immunoparesis between COVID-19-infected pts (43/50, 87%) and COVID-19-non-infected pts (255/301, 85%).

Treatment for multiple myeloma in 50 MM pts with COVID-19 disease

There were four types of anti-myeloma treatment: daratumumab-based therapy (15 pts, 30%), bortezomib-based therapy without daratumumab (17 pts, 34%), lenalidomide-based treatment without daratumumab (12 pts, 24%), other type therapy with novel drugs, such as carfilzomib or pomalidomide (6 pts, 12%). All MM treatments included corticosteroids as a part of treatment (dexamethasone or prednisone). MM staging was carried out according to the

International Staging System (ISS) [16]. Standard criteria were used for the evaluation of MM response [17]. Upon COVID-19 symptom onset, MM treatment was interrupted in all cases.

Clinical manifestation of COVID-19 disease

The clinical manifestation of COVID-19 disease was variable, from mild symptoms of upper respiratory infection without fever treated fully ambulatory to COVID-19 pneumonia with dry cough, dyspnea, fever, and hypoxia and in some cases with respiratory failure. Other non-specific symptoms were arthralgia, myalgia, fatigue, headaches, and diarrhea. All our MM pts with COVID-19 pneumonia (28/50 cases, 54%) were hospitalized. We recognized three types of COVID-19 infection in our set of pts: mild course, treated fully ambulatory, moderate course with hospitalization at standard unit (SU), and severe course with hospitalization at intensive care unit (ICU). No previous anti-COVID vaccination was done in this cohort of pts.

Laboratory and clinical parameters and their possible relationship to COVID-19 outcome

We retrospectively analyzed the main clinical characteristics of MM pts at the time of COVID-19 infection, such as age, gender, ISS stage, type of monoclonal immunoglobulin (MIg), comorbidities, presence of immunoparesis, performance status according to ECOG grade [18], number of myeloma treatment lines, response to the last treatment line, type of treatment line with various novel drugs, and other with aim to find possible relationship to COVID-19 outcome.

Statistics

Descriptive statistics for demographic characteristics and clinical variables were used. Differences between categorical variables were analyzed with Fisher's exact test. A two-sided p value of ≤ 0.05 was considered significant. All statistical analyses were performed using IBM®SPSS® Statistics Version 27.

Results

Patient characteristics

Characteristics of cohort 50 MM pts on anti-myeloma therapy with novel drugs, who suffered from COVID-19 infection, are summarized in Table 1. Median age at time of COVID-19 infection was 68 years (range 41–86). Thirty-two pts (64%) were male; 18 pts (36%) were female (Table 1).

Table 1 Patient characteristics: cohort of 50 MM pts with COVID-19 infection

Parameter—type	Parameter—subtype	All pts: Number (%) 50 (100)	Ambulatory pts: Number (%) 22 (100)	Hospitalized pts: Number (%) 28 (100)
Age in years (median; range)		68; 41–86	66; 41–81	69; 55–86
Gender	Female	18 (36)	7 (32)	11 (39)
	Male	32 (64))	15 (68)	17 (61)
ISS stage	ISS-I and II	39 (78)	16 (73)	23 (82)
	ISS-III	11 (22)	6 (27)	5 (18)
Type of M-protein	IgG	39 (78)	16 (72)	20 (71)
	IgA	8 (16)	5 (23)	6 (21)
	Light chain	3 (6)	1 (5)	2 (8)
Line of MM treatments	1 or 2	37 (74)	19 (86)	18 (64)
	≥ 3	13 (26)	3 (14)	10 (36)
ECOG grade	0–2	40 (80)	21 (95)	18 (64)
	≥ 3	10 (20)	1 (5)	10 (36)
Comorbidities	0 or 1	20 (40)	12 (55)	7 (25)
	≥ 2	30 (60)	10 (45)	21 (75)
Last MM treatment before COVID-19 infection	Daratumumab-based	15 (30)	4 (22)	11 (39)
	Lenalidomide-based	12 (24)	8 (36)	4 (14)
	Bortezomib-based	17 (34)	8 (36)	9 (33)
	Other	6 (12)	2 (6)	4 (14)
Disease status at COVID-19 infection	Responsive disease	33 (69)	19 (86)	15 (54)
	Active disease	15 (31)	3 (14)	13 (46)

Concomitant cardiovascular or pulmonary comorbidities were seen in 46 pts (96%), of which hypertension was the most common (35 pts). Some MM pts had 2 or more comorbidities (30 pts, 60%), such as chronic ischemic heart disease, diabetes mellitus, chronic obstructive pulmonary disease, and others. In our cohort, there were 34 MM pts (68%) in remission of disease (complete remission (CR), very good partial remission (VGPR), or partial remission (PR)) and 16 MM pts (32%) with non-responsive disease (minimal response (MR), stable disease (SD), or progression of disease (PD)).

The laboratory findings included blood count level and value of C-reactive protein and creatinine were available in 32 pts (32/50, 64%) (summarized in Table 2). The analysis of COVID-19-specific antibodies was not done in our group of pts. There were two main types of COVID course in our pts, fully ambulatory course (22 pts, 44%) and course with hospitalization (28 pts, 56%).

Outcome and therapy of COVID-19 infection in MM patients

The COVID-19 treatment in 22 MM pts (22/50, 44%) with ambulatory course of COVID-19 was mostly symptomatic and supportive care with prophylactic use of antibiotics to prevent bacterial superinfection in pts with CRP elevation. All these MM pts recovered completely in median of 22 days

Table 2 Laboratory values at diagnosis of COVID-19 infection in 33 multiple myeloma patients

Parameter	Median; range	Normal range of values
CRP, mg/L	14; 1–300	0–5
Hemoglobin, g/L	105; 84–154	130–170
Leukocytes, 10^9/L	4.7; 2.13–11.3	4–10
Neutrophils, 10^9/L	2.75; 0.82–9.37	2–7
Lymphocytes, 10^9/L	0.795; 0.18–4.09	0.8–4
Thrombocytes, 10^9/L	149; 2–399	150–400
Creatinine, μmol/L	94; 63–540	60–100

(range 20–45); after this, they continued in their anti-myeloma treatment.

In total, 28 MM pts (28/50, 56%) were admitted due to COVID-19 pneumonia. Hospitalization in SD was necessary in 18 pts (18/28, 64% from all COVID-19 hospitalizations); 10 pts (10/28, 36%) were admitted in ICU. Invasive pulmonary ventilation (IPV) was done in 7 pts (7/28, 25%).

Treatment of 28 hospitalized MM pts was variable according to various hospital COVID-19 treatment protocols. All hospitalized pts were treated by oxygen therapy; thromboembolic prophylaxis was done in all pts, too. Regarding treatments used for COVID-19, 12 pts were treated with combination of remdesivir and convalescent

plasma, 12 pts were treated by steroids (mainly dexamethasone or methylprednisolone) and broad-spectrum antibiotics, and in 4 pts, treatment details were unknown.

Full recovery from COVID-19 infection with regression of clinic symptoms and achievement of PCR negativity of COVID-19 was observed in 19 hospitalized MM pts in median of 35 days (range 21–53). Nine pts (9/50, 18%) died due to severe COVID-19 pneumonia with respiratory and multi-organ failure in median of 10 days (range 7–21) from COVID-19 diagnosis. No death to thromboembolic event was observed. Mortality to COVID-19 pneumonia at group of 28 hospitalized MM pts was 32% (9/28 pts).

The COVID-19 infection interrupted anti-myeloma treatment in all 50 pts. After recovery from COVID-19, in median 32 days, 41 MM pts (82%) were able to continue with previous anti-myeloma treatment. In median follow-up of 3 months from COVID-19 infection, 41 MM pts (82%) are alive and COVID-19 free. We recommended anti-COVID-19 vaccination according to the Czech national health guidelines in interval 3 months from COVID-19 infection for all of them.

Clinical and laboratory variables and their relationship to outcome of COVID-19 infections—results of statistical analysis

Some clinical, demographic, and laboratory parameters, such as age, gender, ISS stage, type of monoclonal immunoglobulin (MIg), comorbidities, immunoparesis, performance status according to ECOG [16], number of treatment lines, response to the last treatment line, and other, were evaluated in our cohort of 50 MM pts with the aim to define variables important for adverse outcome of COVID-19 infection resulting in hospitalization or death. The results of statistical analysis are shown in Table 3 for COVID-19 hospitalization and in Table 4 for COVID-19 mortality.

The statistically significant parameters for COVID-19 hospitalization were as follows: responsive versus non-responsive disease ($p = 0.027$), ECOG performance status 0–2 versus ≥ 3 ($p = 0.014$), presence of comorbidities (0–1 versus ≥ 2, $p = 0.043$). None of the other studied risk factors was significantly associated with COVID-19 hospitalization (age, gender, ISS stage, type of anti-myeloma treatment, immunoparesis, blood count values, values of creatinine and C-reactive protein).

The statistically significant parameters for COVID-19 death were as follows: ECOG performance status 0–2 versus ≥ 3 ($p = 0.001$), presence of comorbidities (0–1 versus ≥ 2, $p = 0.007$), serious course of COVID-19 disease with ICU hospitalization (SU versus ICU, $p = 0.001$), and/or invasive pulmonary ventilation treatment (IPV) ($p = 0.001$). None of the other studied risk factors was associated with COVID-19 death (age, gender, ISS stage, immunoparesis,

Table 3 Hospitalization for COVID-19 pneumonia: estimated outcome predictors based on statistical analysis with Fisher's exact test

Parameter	Comparison	*p*-value
Gender	Female versus male	0.559
Age	≤ 65 versus other	0.557
	≤ 75 versus other	0.548
ISS stage	I + II versus III	0.733
ECOG (performance status)	0–2 versus ≥ 3	0.014
Comorbidities	0–1 versus ≥ 2	0.043
Treatment line	1–2 versus ≥ 3	0.104
MM treatment response	Responsive versus active disease	0.013
Type of last MM treatment	Daratumumab-based versus other	0.121
	Lenalidomide-based versus other	0.183
	Bortezomib-based versus other	0.239
Hemoglobin	≤ 100 versus other	0.479
C-reactive protein	≤ 50 versus other	0.141
Thrombocytes	≤ 100 versus other	1.000
Creatinine	≥ 176 versus other	1.000
Immunoparesis	Yes versus no	0.389

type of anti-myeloma treatment, COVID-19 treatment with remdesivir and convalescent plasma).

Discussion

The COVID-19 infection has affected pts globally. However, heterogeneity in outcome of COVID-19 infection has been observed to be associated with presence of comorbidities and cancer. Our retrospective study focused on outcome of 50 outpatient MM pts treated by variable types of novel drug therapy (daratumumab-based, lenalidomide-based, bortezomib-based, or other treatment), who suffered from COVID-19 infection.

The interruption of MM therapy in MM pts with symptomatic COVID-19 disease is strongly recommended [14]. In our cohort of MM pts, anti-myeloma treatment was interrupted for COVID-19 infection in all pts until full recovery from COVID-19 or death.

Optimal treatment of hospitalized MM pts with symptomatic COVID-19 disease is unclear; many pts can receive some novel agents against SARS-Cov-2 with various results [14]. In our hands, 12 hospitalized MM pts with COVID-19 pneumonia were treated with remdesivir and convalescent plasma, 9 pts fully recovered and 3 pts died; the effectivity seems to be relatively high, but our cohort is small and other clinical studies are needed.

Table 4 Mortality for COVID-19 pneumonia: estimated outcome predictors based on statistical analysis with Fisher's exact test

Parameter	Comparison	*p*-value
Gender	Female versus male	0.459
Age	≤65 versus other	0.699
	≤75 versus other	0.423
ISS stage	I+II versus III	1.000
ECOG (performance status)	0–2 versus ≥3	0.001
Comorbidities	0–1 versus ≥2	0.007
Treatment line	1–2 versus ≥3	1.000
MM treatment response	Responsive versus active disease	0.692
Type of last MM treatment	Daratumumab-based versus other	1.000
	Lenalidomide-based versus other	1.000
	Bortezomib-based versus other	0.467
Hospitalization unit type	standard versus intensive care unit	0.001
Type of COVID-19 treatment	Remdesivir+convalescent plasma versus other	1.000
Immunoparesis	Yes versus no	0.258

Adult patients with hematological malignancies and COVID-19 positivity, especially hospitalized pts, have a high risk of dying [19]. Consensus paper from the European Myeloma Network prepared guidelines for therapeutic decisions in the era of the COVID-19 pandemic for MM pts [14]. Oral agent-based regimens should be considered, whereas de-intensified regimens for dexamethasone, bortezomib, carfilzomib, and daratumumab should be used based on a patient's risk and response [14]. Clinical studies have shown that MM pts under treatment with immunomodulatory drugs and proteasome inhibitors are at increased risk of severe infections [20, 21]. However, some reports did not show a correlation between daratumumab or IMID-based systemic therapy and adverse COVID-19 outcome [22, 23].

Immunoparesis is associated with worse overall survival, which is not generally related to an increase risk of infections [11, 24]. In the present cohort, we observed immunoparesis in majority of pts, but we did not see a significant correlation with poor COVID-19 outcome. Similar results have been published previously [1].

Our data suggest no significant relationship between prior lines of anti-myeloma therapy or prior type of therapy with novel drugs (daratumumab, lenalidomide, bortezomib) and outcome of COVID-19. With the limitation of our sample size, there is no clear suggestion for the need to avoid any specific MM treatment with novel drugs in indicated cases. In our hands, after median of interruption of 32 days, anti-myeloma treatment was continued in 82% of pts. Importantly, our MM pts with responsive disease had superior outcome compared with those with non-responsive disease, as has been published previously [11].

In the general population, the probability of dying from COVID-19 has been reported to be between 0.5 and 3% including all COVID-19-positive patients [3]. Recent clinical trials found a higher mortality rate in hospitalized MM pts with COVID-19 (34–39%) [25, 26], when compared to age- and sex-matched hospitalized non-MM pts with COVID-19 (16–23%) [25, 26]. In our cohort of MM pts, mortality for all pts was 18% and for hospitalized pts 32%. Serious course of COVID-19 disease with ICU hospitalization was observed in 36% pts (10/28). Thus, we confirmed previous results of higher mortality in MM pts with COVID-19.

In summary, our MM pts treated with novel drugs show a high risk of morbidity and mortality from COVID-19 infection which seems to be associated predominantly with MM diagnosis, presence of comorbidities, and performance status according to ECOG. None of the other studied risk factors was associated with poor outcome (age, gender, ISS stage, immunoparesis, type of anti-myeloma treatment). No significant correlation with various types of anti-myeloma therapies to outcome of COVID-19 infection was observed in our cohort of 50 MM pts. The course of COVID-19 disease in MM outpatients is mostly moderate or serious with 56% of hospitalizations (28/50) and 18% of deaths (9/50).

As there is currently no specific anti-COVID treatment approved and fully successful, providing anti-COVID vaccinations to all MM pts should be strongly recommended. After recovery from COVID-19 infection, the continuation of anti-myeloma therapy is recommended.

Declarations

Conflict of interest The authors declare no competing interests.

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