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ORIGINAL ARTICLE

Practical management of patients with hematological diseases during the COVID-19 pandemic in Japan

Masao Hagihara[1] · Shin Ohara[1] · Tomoyuki Uchida[1] · Morihiro Inoue[1]

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Abstract
Polymerase chain reaction (PCR) tests cannot always detect the SARS-CoV-2 virus, possibly due to differences in sensitivity between sample types. Under these circumstances, immunochromatography may serve as an alternative method to detect anti-SARS-CoV-2 IgG antibodies that indicate a history of infection. In our analysis of patients with severe COVID-19 infection, we found that 14 of 19 serum samples were positive for IgG antibodies, whereas 6 of 10 samples from patients with asymptomatic or mild cases were negative. Two patients with immune thrombocytopenia who were treated with prednisolone experienced aggressive COVID-19-related respiratory failure and eventually died. Patients not in remission and those who received steroid-based chemotherapy had a higher risk of death, and patients with lymphoid malignancies including lymphoma and myeloma died in larger numbers than those with myeloid malignancies. A stricter cohorting strategy based on repeat PCR tests or isolation to a private room should be adopted in routine care in hematology departments to prevent viral spread to the environment.

Keywords COVID-19 · Nosocomial infection · Anti-SARS-CoV-2 IgG · Survival

Introduction

We decided to write a review on management of patients with hematological diseases during the novel coronavirus (COVID-19) pandemic based on our experience with a large nosocomial outbreak of COVID-19 at our hospital in late Mar 2020, while also incorporating references to currently available evidence, most of which comes from outside Japan.

Forty-eight of the 61 inpatients at our hematology department at the time contracted COVID-19, most of the cases were severe, and ultimately 21 patients died at our hospital [1].

In this review, we will discuss management of COVID-19 based on infection prevention in patients with hematological diseases, a population highly susceptible to viral infection, as well as institutional measures for preventing the spread of COVID-19 when a confirmed case is detected, prediction of which patients will develop severe disease, and treatment of severe disease, while reflecting on our own experience.

Testing

In this section, we will specifically discuss COVID-19 tests designed to detect SARS-CoV-2 to diagnose current infection. As tests that detect pathogens only provide the information of whether or not a pathogen could be detected, one should always keep in mind that this is not necessarily the same as whether or not the person has been infected by the pathogen.

Tests that detect viral genetic material (nucleic acids)

Polymerase chain reaction

A PCR (polymerase chain reaction) test for SARS-CoV-2 was first developed in Jan 2020, and has been covered by the Japanese National Health Insurance since that Mar. PCR tests are the most specific and sensitive of all SARS-CoV-2

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✉ Masao Hagihara
hagihara@eijuhp.com

[1] Eiju General Hospital, Tokyo, Japan

tests currently in use, and are one of the strongest tools for diagnosis of COVID-19.

To maximize the advantages of PCR testing, it is key to use them with an understanding of their flaws and limitations. Here, we share some pitfalls of SARS-CoV-2 PCR testing based on actual experience at our hospital.

False negatives at diagnosis The diagnostic specificity of PCR tests has been reported as over 99%, which poses little issue from an infection control perspective, but the sensitivity varies widely from 30 to 70%. The sensitivity is greatly affected by the timing and site of sample collection, and is associated with changes in viral load in different organs after infection is established [2]. It is believed that the virus typically begins replicating in the upper airway in the early stage of infection, but over time, the viral load in the upper airway decreases as the viral load in the lower airway and other organs increases. Therefore, sensitivity is higher with nasopharyngeal and oropharyngeal swabs in the early stage of infection, and is higher with samples from the lower airway (e.g., sputum and bronchoalveolar lavage fluid) in more advanced infection. Even among samples from the upper airway, sensitivity is lower with oropharyngeal swabs than nasopharyngeal swabs [3]. In the hematology ward of our hospital, we switched from oropharyngeal swabs in late Mar to nasopharyngeal swabs starting in Apr, which led to several successive patients having a positive result on their second PCR test who had a negative result on their first PCR test. Recent research showing that PCR testing with saliva samples has very high agreement with nasopharyngeal swabs (97%) led to widespread adoption of saliva testing at public health centers and private companies [4]. This method is good for infection control because it reduces the risk of viral spread during sample collection.

In estimates based on a mathematical model, the sensitivity of PCR testing with nasal or oropharyngeal swabs was at a maximum of approximately 80% at 2–3 days after symptom onset, but was only 62% on the day of onset and 38% the day before onset. Thus, sensitivity is projected to be low during the time period when transmissibility is high [5]. When we had the large nosocomial outbreak at our hospital, we conducted PCR tests in all our patients, including those without symptoms. We divided patients into three cohorts PCR-positive patients, PCR-negative close contacts, and PCR-negative patients with no contact history. A new mass outbreak occurred among the PCR-negative close contact cohort. We believe this may be because some of the patients in the negative cohort were false negatives, due in part to having a pharyngeal swab for their first test, and that these patients infected those who had not yet been infected [5]. When looking at a negative PCR result, one should always keep in mind the possibility of false negatives and make a comprehensive assessment of infection status with consideration to other information such as contact history, symptoms, and imaging findings (e.g., CT scans).

Persistent positive after symptom resolution This phenomenon is believed to occur because the lower limit of detection for PCR is too low and causes a trace amount of residual viral nucleic acids to be detected even after the virus is no longer clinically active or transmissible. In fact, some cases of long-term persistent positive PCR results despite symptom resolution have been reported [6] and this became a problem that could not be ignored because two consecutive negative PCR results were initially required to discharge patients with COVID-19. Nakamura et al. note how the BR regimen (bendamustine + rituximab) especially extends the duration of a positive result [7]. In recovered patients at our hospital, 16 of the 39 total and 12 of the 18 with hematological diseases required more than 30 days to certify two consecutive negative PCR results.

Although a negative PCR result is no longer a discharge requirement, providers should carefully determine whether or not a persistent positive PCR result truly indicates persistent infection in circumstances where PCR results will be used to decide whether to extend the quarantine period or delay surgery or treatment.

Repeat positive after previous negative Some cases where patients who previously tested negative on PCR tested positive again after a certain period of time have been reported [8–10]. In an Italian study, 16.7% of patients who had recovered from COVID-19 tested positive again at least 2 weeks after their previous negative test (mean time elapsed since initial infection approximately 2 months) (0.11). In asymptomatic cases, the mechanism is likely similar to that for persistent positives as discussed above. However, a new positive accompanied by symptoms suggests recurrence of viral activity and transmissibility, and could occur through either of mechanisms of reinfection or viral reactivation. Whereas two patients with hematological diseases among the five patients at our hospital with repeat positive results had moderate to severe pneumonia, three health care providers without underlying diseases had no symptoms or only mild symptoms. Although this suggests that SARS-CoV-2 can be reactivated in immunodeficient patients, it is unclear whether the reactivated virus can be transmitted to others.

LAMP

LAMP is an alternative test method to PCR that measures nucleic acids and was developed in Japan. It is an abbreviation of loop-mediated isothermal amplification. This method is designed so that the next amplification cycle starts without needing to change temperature between cycles because setting complementary primers at both

ends of the target gene causes the ends of the amplicon to automatically fold over to form a loop. Its advantages are that the analytical mechanism is simpler than that for PCR, and that it yields results quicker than PCR. It is slightly less sensitive than PCR, but is used as a near equivalent to PCR in clinical practice. A study of LAMP for detecting SARS-CoV-2 showed that agreement with PCR was 97.4% (0.12). However, the appropriate sample type must be used because false positives have been reported with some sample types. In a study of cases at our hospital (using 92 samples) we found 88% agreement with PCR, with sensitivity at 70% and specificity at 95%.

Tests that detect viral proteins (antigens)

Qualitative antigen tests (immunochromatography)

This test gives a result with just a simple single-unit kit without requiring any other test equipment by triggering an antigen–antibody reaction using antibodies against SARS-CoV-2 viral proteins [13]. It only takes about several minutes to tens of minutes to get the result, and is the fastest test for detecting the virus. The agreement rate with PCR is 90% or higher if done within 2–9 days after symptom onset, which makes it useful for quickly determining whether a patient with COVID-19 like symptoms needs treatment. Like PCR tests, it can also be done with a saliva sample [14]. Although the Ministry of Health, Labour and Welfare authorizes its use to definitively rule out infection within 2–9 days after symptom onset, one must keep in mind that these tests are expected to have a higher false-negative rate than PCR tests. In our personal opinion, a negative antigen test result should not be casually used to determine the need for isolating a hospitalized patient. It is also clearly a mistake to use these tests for screening of asymptomatic patients because they are never reliable during the period from before symptom onset to the first day of onset or once 10 days have passed since onset.

Quantitative antigen tests (CLEIA)

These tests are similar to rapid test kits in that they use antibodies against viral proteins, but are different in that they quantify the amount of viral proteins using a fully automated immunoassay analyzer [14]. Their sensitivity is higher than immunochromatography and at a similar level to simple nucleic acid tests such as LAMP, but they do not offer the convenience and speed of antigen tests. They offer the advantage of relatively high sensitivity using readily available immunoassay analyzers, but are not a perfect replacement for PCR.

Antibody tests

Several studies from Japan and abroad have investigated antibody tests for COVID-19. A small Japanese study of a SARS-CoV-2 antibody test kit (KURABO Industries Ltd.) using immunochromatography (qualitative) that was developed in China and later marketed as a research reagent in Japan as well showed that all 24 patients infected with the novel coronavirus tested positive for anti-SARS-CoV-2-IgG antibody at a mean time point of 7 days [15]. At our hospital, we also encountered many cases where patients who were strongly suspected to have COVID-19 based on their clinical presentation and course but were not diagnosed due to repeatedly testing negative by PCR had a subsequent positive IgG antibody result suggesting they had been infected. As these findings illustrate, antibody testing is very useful as a complement to PCR testing or to determine the rate of spread among a group (i.e., for surveillance) (0.16). Chemiluminescent microparticle immunoassay has the advantage of assessing quantitatively antibody titers. The main target antigens are the nucleocapsid protein (N) and spike protein (S), and analytical systems that use the latter offer the capability of detection soon after infection [17].

Studies from China [18, 19] have shown that patients with severe disease have a stronger antibody reaction than those with non-severe disease, and antibody titers do not differ between age groups [19].

Studies on antibody retention have reported results of analysis of convalescent serum collected over time during the nearly 1-year period since COVID-19 first emerged in China.

A Canadian study of 15 patients showed that antibody titers begin to decline rapidly around 3 months after symptom onset [20]. A similar study from China [18] showed that IgG antibodies were lost in 12.9% of symptomatic PCR-positive individuals and 40% of asymptomatic PCR-positive individuals in the recovery stage (2–3 months after infection). An American study also showed that antibody titers decline with time over a 4-month period in individuals with mild symptoms [21]. These results will be important evidence for developing convalescent serum therapy going forward.

A study in severe acute respiratory syndrome (SARS) showed that positive ELISA antibody test results persist for 24 months after infection [22]. A study that followed nine survivors of Middle East respiratory syndrome (MERS) found that antibodies were retained in 5 of 6 symptomatic patients at 3 months and 4 of 5 patients at 10 months, and that all three asymptomatic patients tested negative for antibodies [23]. The latest research on retention of neutralizing antibodies against COVID-19 from Yokohama City University (unpublished) and outside Japan show that antibody titers do not decline for at least 4 months [16]. Further

building of this body of knowledge on the relationship between antibody retention and infection risk will undoubtedly provide critical information for vaccine development as well.

Few studies have investigated acquisition of anti-SARS-CoV-2 IgG antibodies or prevention of severe COVID-19 in patients with hematological diseases. In a study of chronic lymphocytic leukemia, which is prevalent in the West, 14 of 21 infected patients (67%) tested positive for antibodies, and 78% of patients with severe COVID-19 and 58% of patients with non-severe COVID-19 tested positive. In addition, hypogammaglobulinemia was negatively correlated with antibody positivity [24]. A similar antibody positivity rate (69%) has been reported for patients with multiple myeloma [25].

Studies have also investigated whether rituximab inhibits antibody acquisition. Most notably, a Japanese study showed that patients experiencing hypogammaglobulinemia during rituximab maintenance therapy had lingering pneumonia for 2 months after infection, and continued to test negative for antibodies during that period [26].

When we determined IgG antibody status by immunochromatography using samples from patients with hematological diseases at our hospital, we found that approximately 70% (14 of 19) of those who developed pneumonia but only 40% (4 of 10) who had no symptoms or mild symptoms (e.g., only fever without pneumonia) were antibody positive at a mean period of 1 month after infection. Two antibody-negative patients had a repeat positive PCR result and developed pneumonia approximately 2–4 weeks after getting a negative PCR result (i.e., after recovery) (0.27). Patients with hematological diseases can show a very poor immune response to COVID-19, and thus when resuming chemotherapy in a patient who had COVID-19 it is important to know whether they acquired and/or retain antibodies.

Management of specific diseases

Benign diseases

Aplastic anemia (AA)

Use of corticosteroids to treat autoimmune disorders, and particularly connective tissue diseases such as rheumatoid arthritis, is known to increase risk of hospitalization for COVID-19 and severe COVID-19, but use of biologics such as anti-TNF-α antibodies was shown to not be a risk factor [28]. Although immunosuppressants such as cyclosporine are the mainstay of therapy for AA, even the American Society of Hematology (ASH) recommendations do not raise any particular concerns because of those findings.

Immune thrombocytopenic purpura (ITP)

Four of eight patients (50%) at our hospital with benign disease who were taking prednisolone at a dose of 10 mg/day or higher died. This included two patients who were taking relatively high doses of prednisolone (0.5 mg/kg/day) after admission for newly diagnosed ITP.

Based on our experience with such patients who contracted COVID-19 and developed severe symptoms while on prednisolone, we changed the policy of our hospital for management of new ITP from maintaining prednisolone at the initial dose for 2 or 4 weeks to a new policy emphasizing prompt response to treatment by starting with high-dose dexamethasone (20–40 mg/day for 4 days) as the first-line drug and then switching to a thrombopoietin-receptor agonist (TPO-RA) as the second-line drug relatively quickly if dexamethasone therapy is not effective within about 2 weeks.

Both the ASH and British Journal of Haematology (BJH) guidance [29] state that TPO-RAs should be considered as first-line drugs for ITP during the COVID-19 pandemic. However, Japanese treatment guidelines for ITP published in 2019 only list steroids as a first-line option, and use of other drugs is also restricted due to lack of insurance coverage.

If a patient with untreated ITP develops COVID-19, it is reasonable to start treatment of ITP with a relatively low dose regimen of prednisolone (20 mg/day), such as one described in the BJH guidance, based on the fact that steroids have not been proven to directly worsen the course of COVID-19. [30]. Several studies have shown that thrombosis is involved in development of severe COVID-19 in patients who do not respond well to steroids [31, 32]. A relatively large percentage of patients with ITP experience thrombosis as a complication, [33] and the risk of thrombosis developing as an adverse event cannot be ignored [34]. Consequently, the decisions of whether to start TPO-RA therapy and what dose to use must be made with care. A randomized controlled trial showed that a short course of dexamethasone (6 mg/day for 10 days) reduces mortality risk in patients in whom pneumonia progresses to respiratory failure (who are started on oxygen therapy) (0.35). This indicates that aggressive treatment with dexamethasone can be considered regardless of the disease.

In the case of chronic ITP, most patients are tapering off prednisolone or on maintenance therapy, and based on experience at our hospital we believe that rapidly reducing or stopping steroid therapy risks worsening the cytokine storm, which is why we recommend following the BJH guidance and continuing current therapy as-is.

Malignant diseases

Table 1 shows results of analysis for the population of patients with hematological malignancies who were infected

Table 1 Demographics and baseline characteristics of patients with coronavirus disease 2019 and odds ratio of death

	Died	Recovered	Odds ratio	*p* value
Total	21	13		
Sex				
Male	10	9	0.415 (0.070–2.102)	0.296
Female	11	4		
Age				
≥ 70	16	11	0.591 (0.048–4.471)	0.682
< 70	5	2		
≥ 80	6	3	1.322 (0.216–10.099)	1
< 80	15	10		
Disease				
Cancer	19	12	0.797 (0.012–16.907)	1
Not cancer	2	1		
Treated with steroids in past 1 month				
Yes	12	4	2.901 (0.573–17.369)	0.172
No	9	9		
Lymphocytes, (µl)				
< 1000	17	8	2.576 (0.425–17.009)	0.254
≥ 1000	4	5		
White blood cell count (µl)				
< 4000	8	6	0.725 (0.143–3.668)	0.728
≥ 4000	13	7		
Lactate dehydrogenase, units per l				
≥ 250	7	3	1.642 (0.281–12.286)	0.704
< 250	14	10		
Treated with favipiravir				
Yes	13	7	1.379 (0.273–6.990)	0.728
No	8	6		
Treated with nafamostat mesylate				
Yes	14	6	2.273 (0.455–12.105)	0.296
No	7	7		
Treated with ciclesonide				
Yes	8	6	0.725 (0.143–3.668)	0.728
No	13	7		
Remission				
No	17	5	10.758 (1.459–138.874)	0.0118
Yes	2	7		
Origin of tumor				
Lymphoid	14	5	3.734 (0.667–23.879)	0.13
Myeloid	5	7		
Chemotherapy				
With prednisolone	12	3	8.350 (1.111–88.068)	0.0344
Without prednisolone	3	7		
Hypertension				
Yes	10	3	2.933 (0.535–21.415)	0.2763
No	11	10		
Diabetes				
Yes	7	4	1.121 (0.206–6.814)	1
No	14	9		

at our hospital (who died at our hospital or were treated before discharge), excluding those who were asymptomatic or were transferred. The mortality rate was significantly higher in patients not in remission (including those not yet confirmed to be in remission) compared with those in remission. The rate was also higher in patients undergoing chemotherapy including a steroid versus chemotherapy not including a steroid.

A recent review (meta-analysis) of mainly non-Japanese studies published in the journal Blood showed that the survival rate among 3377 total patients was 34% (0.36). The reason why the outcomes at our hospital were especially poor is that they were part of a nosocomial outbreak (first report) and, as mentioned before, our rate excludes asymptomatic patients.

The sub-analyses by disease discussed below are different: they include all patients diagnosed with COVID-19 at our hospital.

Acute leukemia (AML/ALL) and myelodysplastic syndrome (MDS)

One ALL patient who was not in remission and had progressive disease was infected and died, and 4 of 12 patients with myeloid lineage tumors died (Table 2, 33%). Three AML patients in remission who were receiving induction/consolidation therapy (none on azacitidine therapy) were infected sometime between the myelosuppression stage and hematological recovery, and none of these patients developed severe COVID-19. In addition, two patients not in remission who were on salvage therapy were asymptomatic, excluding one patient with progressive disease. A non-Japanese study comparing risk by disease found that AML patients are in the high-risk group [37]. Although our patient characteristics and sample size differed from this study, at our hospital we found a higher mortality rate for patients with the lymphoid malignancies discussed in the following sections (particularly lymphoma and myeloma).

At our hospital, we mainly use azacitidine to treat high-risk MDS or AML/MRC. In our analysis, three of seven inpatients with COVID-19 died. Both of the two AML patients who had achieved hematological improvement survived, but the three patients (two AML, one MDS) whose neutrophil count at onset was less than 500/mm^2 all died.

The cause of death could have been respiratory failure associated with COVID-19, but we could not rule out involvement of secondary bacterial infection related to a low neutrophil count. Antibiotics (we also used them in our patients) and aggressive granulocyte-colony stimulating factor (G-CSF) therapy could also be considered.

The ASH recommendations state that although there is a theoretical concern that G-CSF therapy could exacerbate the respiratory effects of COVID-19, it should be strongly considered to shorten the duration of neutropenia and reduce risk of febrile neutropenia. They also consider it unnecessary to set a low initial intensity of chemotherapy based on concern about myelosuppression.

Malignant lymphoma

As shown in Table 3, COVID-19 outcomes for malignant lymphoma at our hospital were exceedingly poor. Almost all (15 of 16) of the infected inpatients, including those transferred to another institution, had not yet been confirmed

Table 2 Clinical characteristics and outcome of patients with myeloid malignancies during SARS-CoV-2 outbreak at our institution

Case	Age	sex	Diagnosis	Disease status	Regimen	Number of cycles	Neutro (/mm^2)	Lymph (/mm^2)	Treatment for COVID-19	Outcome
1	70	M	AML (M4)	RR	ACR/AraC	1	2000	580	No	A
2	69	M	AML (M4)	RR	HD-AraC	1	1100	907	No	A
3	47	M	AML (M2)	ND	A-tripleV	1	1600	980	No	A
4	73	M	AML/MRC	RR	VP-16 p.o		2800	650	F	D (21)
5	72	M	AML/MRC	ND	MIT/AraC	1	5700	632	No	A
6	79	F	AML/MRC	RR	AZA	1	400	248	No	D (5)
7	78	M	AML/MRC	ND	AZA	7	4400	432	F, N	A
8	69	F	AML	ND	AZA	3	200	250	Unknown	D
9	81	F	AML	ND	AZA	7	1500	816	F, N	A
10	89	F	MDS/MLD	ND	AZA	1	200	544	F, N	D (16)
11	72	M	MDS-EB2	ND	AZA	9	800	209	F, N	A
12	81	F	MDS-EB2	ND	AZA	6	600	1080	F	A

The number in parentheses indicates days after the onset of symptoms or a positive SARS-CoV-2 test result

F female, *M* male, *ND* newly diagnosed, *RR* relapsed and refractory, *ACR* aclacinon, *AraC*, cytarabine, *AZA* azacitidine, *A-tripleV* cytarabine + VP-16 + vincristine + vinblastine, *MIT* mitoxantrone, *F* favipiravir, *N* nafamostat, *A* alive, *D* dead

Table 3 Clinical characteristics and outcome of patients with lymphoma during SARS-CoV-2 outbreak at our institution

Case	Age	Sex	Diagnosis	Disease status	Regimen	Number of cycles	Neutro (/mm^2)	Lymph (/mm^2)	IgG (mg/dl)	Treatment for COVID-19	Outcome
1	89	F	DLBCL	ND	R-CHOP	1	2000	640	No data	F, N, S	D (13)
2	80	F	DLBCL	ND	R-CHOP	2	4600	426	905	F, N	D (20)
3	70	M	AITL	ND	CHO	3	1200	224	No data		A
4	66	F	DLBCL	RR	CHASER	2	600	57	431	F, N	D (20)
5	78	F	DLBCL	RR	no	1	5500	1357	2825	F, N	D (22)
6	73	M	AITL	ND	no	No	1700	313	No data	N	D (9)
7	71	M	DLBCL	RR	R-GCD	2	1200	425	639	F, N	D (9)
8	73	M	DLBCL	ND	R-CHOP	6	2300	723	No data	F, N	D (27)
9	71	F	PTCL	RR	BV	1	8900	480	No data	F, S	D (21)
10	80	M	DLBCL	ND	R-MVP	2	1300	1818	No data		A
11	74	M	DLBCL	ND	R-CHO	1	3400	772	1594	F, N	A
12	53	M	ALCL	ND	A-CHP	2	7500	408	1062		D
13	56	M	MCL	RR	BR	1	1400	627	902		D
14	72	M	DLBCL	ND	No	No	1000	569	2586		D
15	75	F	WM/LPL	RR	BR	1	1100	286	918		A
16	25	F	DLBCL	ND	R-CHOP	1	1900	494	967		A

The number in parentheses indicates days after the onset of symptoms or a positive SARS-CoV-2 test result

F female, *M* male, *ND* newly diagnosed, *RR* relapsed and refractory, *R-CHOP* rituximab cyclophosphamide adriamycin, vincristine prednisolone, *CHASER* cyclophosphamide high-dose cytarabine dexamethasone VP-16 rituximab, *GCD* gemcitabine carboplatin dexamethasone, *MVP* methotrexate vincristine procarbazine, BV brentuximab vedotin, *A-CHP* brentuximab vedotin cyclophosphamide adriamycin prednisolone, *BR* bendamustine rituximab, *F* favipiravir, *N* nafamostat, *S* steroid hormone, *D* dead, *A* alive

to be in remission (were undergoing induction or salvage therapy), and 11 of them died (including one patient in remission). Thirteen had undergone chemotherapy (were in a rest period), and nine of them had undergone a regimen that included a corticosteroid. Four of the six patients who underwent chemotherapy without a steroid survived, whereas six of seven who underwent chemotherapy including a steroid died. This indicates that chemotherapy regimens that include a steroid may have been a risk factor for death as we observed for malignancies overall. We also looked specifically at rituximab therapy, which is a strong contributor to immunodeficiency. Six of 10 patients undergoing rituximab-based chemotherapy (no rituximab monotherapy) died. Notably, of those patients on rituximab-based chemotherapy, five of six patients whose regimen included a steroid died (including four on R-CHOP, one of whom was a woman in her 20s who was infected after primary therapy and developed pneumonia but it resolved) but three of four patients whose regimen did not include a steroid recovered. One of these patients (Case 11) who did not develop severe COVID-19 and recovered despite developing pneumonia, was not treated with prednisolone (received R-CHO instead) due to being a hepatitis B carrier. Based on our experience as described above, we selected a dosing method that reduces the steroid dose below the normal level (normal dose only on the first day, and no steroid from day two onward) for patients with B cell lymphoma who continued inpatient treatment while avoiding infection. We propose this as a safety measure for outpatient treatment as well whenever COVID-19 is spreading rampantly.

Multiple myeloma (MM)

Multiple myeloma is widely known to be associated with particularly high infection risk even among blood cancers. Reasons for this are (humoral) immunodeficiency typified by immunoparesis associated with MM and effects of therapy that has been prolonged by recent introduction of new drugs. An analysis of the latest International Myeloma Society Dataset showed a high mortality rate of 34% in 650 patients with plasma cell malignancies, and multivariate analysis identified advanced age, high-risk MM, renal complications, and poorly controlled MM as unfavorable prognostic factors [38].

Table 4 breaks down results for the small number of patients from our hospital. The most distinctive finding from this group was that five of nine patients died in a very short median period of only 10 days. In addition, three of four patients who had undergone at least five prior regimens died, whereas the two patients who achieved a deep response (very good partial remission or better) recovered. Both of the two patients who were about to start treatment or whose

Table 4 Clinical characteristics and outcome of patients with multiple myeloma during SARS-CoV-2 outbreak at our institution

	Age	Sex	Subtype	Disease status	Duration of disorder (months)	Number of prior regimens	Most recent regimen	Duration of treatment (months)	Outcome	Severity	Treatment for COVID-19	Anti-COV-2 IgG Ab	Outcome
1	87	F	BJP-λ	ND	< 1	No	No	No	SD	AS	No	Pos (32)	A
2	69	M	BJP-κ	RR	97	5	ILd	< 1	PR	C	No	n.d	D (10)
3	85	F	BJP-κ	RR	66	13	VTD-PACE	< 1	PD	C	F, N, S	Neg (12)	D (16)
4	70	F	BJP-λ	RR	33	5	Cd	1–2	VGPR	S	F, N, G, S	Pos (18)	A
5	65	M	IgA-κ	ND	2	1	BRd	1–2	PR	C	F, N, G	Neg (7)	D (10)
6	72	M	BJP-κ	RR	2	7	EPd	< 1	PD	C	N	n.d	D (4)
7	71	M	IgG-κ	ND	< 1	1	DLd	< 1	PR	M	F, N, G	Pos (44)	A
8	68	M	IgA-κ	ND	2	1	Bd	< 1	PR	C	F, N, G, S	Neg (12)	D (19)
9	71	M	BJP-λ	RR	43	3	PBd	4	VGPR	S	S	Pos (36)	A

The number in parentheses indicates days after the onset of symptoms or a positive SARS-CoV-2 test result

F female, *M* male, *ND* newly diagnosed, *RR* relapsed and refractory, *ILd* ixazomib lenalidomide dexamethasone, *VTD-PACE* combined chemotherapy with bortezomib thalidomide dexamethasone cisplatin etoposide and cyclophosphamide, *Cd* carfilzomib dexamethasone, *BLd* bortezomib lenalidomide dexamethasone, *EPd* elotuzumab pomalidomide dexamethasone, *DLd* daratumumab lenalidomide dexamethasone, *Bd* bortezomib, dexamethasone, *BPd* bortezomib pomalidomide dexamethasone, *SD* stable disease, *PR* partial remission, *PD* progress of disease, VGPR very good PR, *AS* asymptomatic, *M* mild, *S* severe, *C* critical, *F* favipiravir, *N* nafamostat, *G* gammaglobulin, *S* steroid hormone, *A* alive, *D* dead

primary induction therapy was suspended due to infection shortly after initiation survived. All four surviving patients tested positive for anti-SARS-CoV-2 IgG antibodies.

In the ASH recommendations, dose reduction of steroids (primarily dexamethasone), switching intravenous therapy to oral therapy in consideration of frequency of hospital visits, and postponing autologous transplantation. However, at least as long as the pandemic continues to not be as widespread in Japan as in the West, we believe that it is important to generally not deviate too greatly from the normal course of treatment aimed at achieving deep remission as quickly as possible.

Infection prevention measures

COVID-19 is primarily transmitted by droplets and contact, but is also believed to be transmissible through aerosols. WHO recommends that standard preventive measures be implemented with all patients, and that measures against droplet and contact transmission be implemented with patients suspected to have COVID-19. In particular, having both patients and providers wear masks may have a synergistic effect in reducing each party's risk of infection [39, 40]. They also recommend to implement measures to prevent air contamination during procedures that could generate aerosols. They repeatedly emphasize the importance of ventilation, and ventilating every certain number of hours even in the winter is useful for reducing risk. It is believed that approximately 30% of infected individuals are asymptomatic carriers [41] and in areas where there is community spread, it is worth considering PCR testing all patients on admission even if asymptomatic (we do this at our hospital). Another approach to consider is to admit any urgently admitted patients to a "pool ward" where they are treated as COVID-positive rather than the relevant ward until they are confirmed to have a negative PCR result. The median incubation period for COVID-19 is generally reported to be 5 days (maximum of approximately 14 days) (0.42). Since it is not possible to avoid admissions during the incubation period, it is necessary to carefully evaluate any fever or respiratory symptoms that occur within 14 days of admission.

It is believed that patients with hematological diseases often must be treated as having suspected COVID-19 because even if they have a neoplastic fever or non-neoplastic disease, their risk of fever is high due to their abnormal immune function. When a patient is suspected to have COVID-19, they must be isolated promptly. It is best that they be placed in a negative pressure room rather than a positive pressure cleanroom.

When an inpatient is confirmed to have COVID-19, any contacts they had such as patients sharing their room or assigned nurses and doctors should be identified promptly.

COVID-19 is considered most transmissible during the period 2 days before symptom onset to shortly after onset, four and thus the patient's contacts prior to developing symptoms must be identified. One study showed that transmissibility is low 5 days after onset and later [43]. When nosocomial infection is detected, a cohorting approach like the one we described above is also necessary. However, at our hospital, there were many false-negative patients among close contacts of positive patients, which suggests that spread might occur through droplets or contact within a shared room. Therefore, keeping close contacts in private rooms whenever possible should minimize the spread of infection. In cases of large nosocomial outbreaks like the one at our hospital, a flaw with the facilities (small number of private rooms) may have exacerbated the spread of infection. Although we were not able to do so at the time, prompt repetition of PCR testing could be valuable [44].

As patients' family members may have COVID-19, it is also necessary to make considerations to prevent infection when explaining the patient's condition to family members in person and for deathbed visits. At our hospital, we use video conferencing.

In addition, it is probably safer for providers caring for COVID-19 patients to avoid caring for other patients because they might transmit COVID-19 to them. Providers must also be proactive about taking off work when they are feeling unwell. We health care providers must imagine ourselves to always be a possible vector for COVID-19, and should behave accordingly to prevent the spread of infection.

Declarations

Conflict of interest The author declares that they have no conflicts of interest.

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