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The effect of the response to the coronavirus disease pandemic on treatment outcomes in patients with lymphoma and multiple myeloma

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Background/Aims: Relatively little data are available on how the response to the coronavirus disease 2019 (COVID-19) pandemic has affected treatment outcomes in patients receiving chemotherapy for lymphoma or multiple myeloma. We aimed to determine the effect of COVID-19 countermeasures on treatment outcomes in this patient population.

Methods: We retrospectively analyzed data on patients treated for lymphoma or multiple myeloma in two tertiary hospitals in Seoul. Patients were divided into two groups: group 1 included patients who received chemotherapy between September and December 2019 (the control period), and group 2 included patients who received chemotherapy between September and December 2020 (the study period). Countermeasures to COVID-19 were applied to the patients in group 2. The countermeasures implemented included mask wearing and regular handwashing at home and in hospital; COVID-19 risk assessments on all hospital visitors; and pre-emptive COVID-19 screening for all newly hospitalized patients and their resident guardians.

Results: No differences in treatment outcomes, including treatment response, incidence and duration of neutropenia or neutropenic fever, delays in chemotherapy, or number of deaths during chemotherapy, were observed between the g roups. None of the patients in group 2 tested positive for COVID-19, and there were no COVID-19-related deaths during the study period.

Conclusions: Countermeasures to COVID-19 did not affect treatment outcomes in patients receiving chemotherapy for lymphoma or multiple myeloma. Data on the effect of countermeasures to COVID-19 on treatment outcomes should continue to be analyzed to ensure that treatment outcomes are not adversely affected.

Keywords: Treatment outcome; Lymphoma; Multiple myeloma; Coronavirus

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense single-stranded RNA virus transmitted via respiratory droplets (direct contact) and contaminated objects and airborne contagion (indirect contact) [1,2]. Although the mortality rate of COVID-19, at approximately 3%, is lower than that of SARS-CoV-1, at approximately 10%, or Middle East respiratory syn-

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drome, at approximately 40%, it is far more contagious, infecting approximately 10 times more people [3]. As the number of patients with COVID-19 increases, the strain on medical resources locally and globally is reaching a level unprecedented in recent times. As various efforts to contain the spread of COVID-19, to produce vaccines against it, and to develop therapeutic agents to treat it are underway, the pressure on medical facilities remains challenging as the need to optimally treat patients with COVID-19 is added to the need to optimally treat patients with other diseases, including malignancies.

Patients with malignancies are more likely to be infected by SARS-CoV-2 and are more likely to develop severe COVID-19 [4,5]. The mortality rate among patients with existing malignancies and COVID-19 can reach approximately 33% [6-10]. The risks of more severe disease and death tend to be higher in patients with hematologic malignancies [11,12], with the mortality rate reported to be as high as 62% [13,14]. Despite the challenges of COVID-19, chemotherapy for patients with hematologic malignancies cannot be delayed indefinitely. Countermeasures to prevent infection with SARS-CoV-2 are thus critical to ensure optimal treatment for both patients with COVID-19 and those with hematologic malignancies receiving chemotherapy.

This study aimed to analyze an example of countermeasures to COVID-19 and to evaluate the impact of these countermeasures on treatment processes and outcomes in patients who were hospitalized repeatedly and/or received outpatient treatment for lymphoma or multiple myeloma.

METHODS

Study design and patients

The study was approved by the appropriate Institutional Review Board (IRB) of Korea University Anam Hospital and Korea University Guro Hospital, and all data were fully anonymized (IRB No. 2020AN0559 and 2021GR0051). As this study was conducted using anonymous patient data, the requirement for informed consent was waived by the IRB.

In this non-interventional comparative cohort study, we retrospectively analyzed the data of patients who were consecutively enrolled in the Lymphoma and Myeloma Registry from September 2019 to December 2019 and from September 2020 to December 2020. Data from two tertiary hospitals affiliated with the Korea University Medical Center (Anam and Guro Hospitals) located in Seoul were used. The Anam and Guro Hospitals had a total of 1,048 and 1,075 beds and received approximately 3,665 and 3,985 outpatients daily, respectively, as of January 2021. Patients who met the following criteria were included: (1) a diagnosis of lymphoma or multiple myeloma according to the World Health Organization classification, and (2) provision of chemotherapy from September 2019 to December 2019 (the control period) or September 2020 to December 2020 (the study period).

Patients were divided into two groups: group 1 included patients with lymphoma or multiple myeloma who received chemotherapy during the control period, and group 2 included patients with lymphoma or multiple myeloma who received chemotherapy during the study period. Countermeasures to COVID-19 were applied to group 2. Group 1 was included as a control group to account for seasonal viral infectious diseases, such as influenza, that may have occurred in patients treated at a similar time before the COVID-19 pandemic. Both groups were defined as patients with lymphoma or multiple myeloma who received chemotherapy within a limited period, and the clinical outcomes measured within the period were compared.

Countermeasures to COVID-19 from September 2020 to December 2020

The South Korean government initiated active quarantine to control the COVID-19 pandemic in February 2020. With the continuation of the COVID-19 pandemic, the two tertiary hospitals in this study also initiated active responses to the COVID-19 pandemic that applied to patients, their guardians, and hospital workers from September 2020. The countermeasures that were implemented and included this study are listed in Table 1.

Patients and their guardians were required to wear a mask, irrespective of whether they were indoors or outdoors at home or in a hospital, and to practice hand hygiene by washing their hands thoroughly with soap under running water. All patients and guardians who visited the hospital were permitted to enter only after confirming that they had no history of visiting any areas with COVID-19 outbreaks or foreign countries, no

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Table 1. Countermeasures to COVID-19 included in this study

Patients and their guardians	General principles Patients and their guardians should wear a mask, indoors or outdoors (at home or in a hospital), and should not touch their eyes, nose, or mouth with unwashed hands. In addition, patients should practice hand hygiene by washing their hands thoroughly with soap under running water. Patients and their guardians should refrain from visiting crowded places and going outside and avoid contact with people who have fever or respiratory symptoms.
Hospital	For patients or visiting guardians All patients and visiting guardians are allowed to enter the hospital only after completing a questionnaire detailing any recent travel to foreign countries or areas where outbreaks of COVID-19 have occurred, as well as any COVID-19-related symptoms, and after confirming the absence of fever (temperature above 37.5°C). All patients newly admitted via emergency rooms, clinics, or other hospitals must be confirmed to be negative for COVID-19 1–7 days before their hospitalization. Resident guardians must also be confirmed to be negative for COVID-19 1–7 days before the patient's hospitalization. Patients are prohibited from leaving the hospital during their hospitalization. Patients and their guardians should avoid unnecessary movement during hospitalization and should refrain from using lounges and restaurants in the hospital. Even if the COVID-19 test was negative before hospitalization, should patients or their guardians develop fever or respiratory symptoms during their hospitalization, the Department of Infectious Diseases should be consulted regarding the need for additional COVID-19 tests. For hospital workers All hospital workers are required to follow quarantine regulations, such as wearing a mask and practicing hand hygiene at the hospital. When COVID-19-related symptoms occur, hospital workers must cease working and undergo prompt diagnostic testing. Unnecessary events or meetings inside and outside the institution are restricted, and if unavoidable, such events or meetings must be confirmed and approved by the department in charge of COVID-19 management. At least the following conditions must be met: (1) attendee list management; (2) sufficient space between seats to ensure physical distancing between all participants; (3) no meals in conference rooms; and (4) wearing of a mask while attending. For those who test positive for COVID-19 Those who test positive for COVID-19 are transferred to nationally designated COVID-19 hospitals or residential treatment centers.
Government [26][a]	Infection prevention and control of foreign nationals Asymptomatic South Korean and foreign nationals on long-term visas are subject to self-quarantine of 14 days (Self-Quarantine Safety Protection App to be installed) and testing at a public health center within 3 days of arrival. Asymptomatic foreign nationals on short-term visas are subject to facility quarantine of 14 days (Self-Diagnosis App to be installed) and testing at a public health clinic within 14 days. If travelers exhibit fever or respiratory symptoms at entry screening, they are tested for COVID-19. South Korean or foreign nationals who test negative are placed under self-quarantine of 14 days (Self-Quarantine Safety Protection App to be installed) or are quarantined at a facility for 14 days (Self-Diagnosis App to be installed). Travelers who test positive for COVID-19 are transferred to nationally designated COVID-19 hospitals or residential treatment centers. Preventing the spread of the virus through epidemiological investigations and quarantine of contacts The central and local governments respond to COVID-19 cases by tracing the source of infection through prompt epidemiological investigations and quarantine of contacts. The contacts identified during the investigation are required to attend healthcare education, have their symptoms monitored, and remain in self-quarantine. Family members, housemates, and other contacts identified by epidemiological investigations on the patient's travel and infection routes are subject to self-quarantine for the maximum incubation period (14 days) beginning from the day after the date of contact with a confirmed patient and should have their symptoms monitored. The Ministry of Interior and Safety and local governments thoroughly manage those under self-quarantine on a one-to-one basis.

[a]The contents have been summarized by extracting information provided on the official website of the Ministry of Health and Welfare of South Korea.

COVID-19-related symptoms, and no fever (temperature > 37.5°C). If one or more of the above conditions were not satisfied, they were not permitted to enter the hospital and were referred to an outdoor COVID-19 clinic or emergency department. All newly admitted patients and their resident guardians were confirmed to be negative for COVID-19 1 to 7 days before hospitalization. Hospitalized patients were prohibited from going out and were to avoid the use of lounges or restaurants in the hospital. When fever and respiratory symptoms occurred in patients or hospital workers, active consultation with the Department of Infectious Diseases to arrange for COVID-19 testing was undertaken. All COVID-19 tests were conducted at the outdoor COVID-19 clinic or emergency department, thoroughly separated from the existing laboratory. If emergency hospitalization was required, dedicated quarantine beds were used until the COVID-19 test result was confirmed. During this period, COVID-19 testing was conducted using a real-time PCR assay (Allplex™ 2019-nCoV Assay, Seegene, Seoul, Korea; or STANDARD M nCoV Real-Time Detection kit, SD biosensor, Suwon, Korea). All test results were recorded within 12 hours. Those who tested positive for COVID-19 were transferred to nationally designated COVID-19 hospitals or residential treatment centers.

Clinical endpoints

The primary endpoints were treatment outcomes under the countermeasures implemented during the COVID-19 pandemic. Treatment outcomes were evaluated as the result of the treatment response evaluation within the corresponding period for each group. If the treatment response evaluation was performed more than twice within the corresponding period for the group, it was summarized based on the best response. The treatment response evaluation for lymphoma and multiple myeloma was assessed according to the Lugano classification [15] and International Myeloma Working Group response criteria [16,17], respectively.

The secondary endpoints were the incidence and duration of neutropenia and neutropenic fever, delays in chemotherapy, mortality during chemotherapy, and the rate of positive COVID-19 results among the tested patients. To evaluate any adverse events, all events that occurred within the corresponding period in each group were counted. Neutropenia was defined as the absolute neutrophil counts (ANCs) < 1,000/μL after chemotherapy. Neutropenic fever and its duration was defined as the time period during which the following conditions were met: (1) development of fever after chemotherapy; (2) an ANC < 500/μL or an ANC < 1,000/μL with a predicted decline to ≤ 500/μL within the next 48 hours; and (3) a temperature of > 38.3°C once, or > 38.0°C sustained over a 1 hour period [18]. A delay in chemotherapy was defined as a delay of ≥ 3 days compared with the scheduled chemotherapy date.

Statistical analyses

Mean values and standard deviations were reported for continuous variables, and percentages were reported for categorical values. Baseline characteristics were compared between the groups using the Mann–Whitney *U* test or chi-square test, according to the type of variable. Equivalence was concluded if the two-sided 90% confidence interval (CI) for the difference in clinical endpoints between the two groups was within the equivalence margin of ± 15% (two-one-sided *t* tests). In the existing equivalence comparison studies, the range of the equivalence margin was 10% to 20%, and a median value of 15% was determined in this study [19-22]. The median number of neutropenia or neutropenic fever episodes and their median durations were compared using the Mann–Whitney *U* test. IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. A p value < 0.05 was set as significant.

RESULTS

COVID-19 pandemic status in South Korea during the study period

Based on the national statistical data for 2019, the total area of South Korea is 100,401 km², with a total population of 51,709,000 inhabitants. The total area of Seoul is 605 km², accounting for only 0.6% of South Korea. However, 18.7% of the total population resides in Seoul, and the population density per km² is 15,964 inhabitants, which is considerably higher than that in other regions and countries (Supplementary Fig. 1) [23-25]. As of January 1, 2021, the cumulative number of confirmed COVID-19 cases in South Korea was 61,769, of which

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19,363 were reported in Seoul, accounting for 31.3% of the total number of confirmed cases (Supplementary Fig. 2) [26-28]. The number of newly reported COVID-19 cases and number of deaths from COVID-19 during the study period in Seoul are summarized in Supplementary Fig. 3 [26,27].

Patient characteristics

In total, 202 patients with lymphoma and 174 patients with multiple myeloma were analyzed in this study (lymphoma, group 1 [n = 97], group 2 [n = 105]; multiple myeloma, group 1 [n = 91], group 2 [n = 83]). Baseline characteristics are summarized in Tables 2 and 3.

Table 2. Baseline characteristics of patients with lymphoma

Baseline characteristic	Group 1 (2019) (n = 97)	Group 2 (2020) (n = 105)	*p* value
Age, yr	60 (13–90)	65 (13–91)	0.207
Sex ratio, male:female	1.37	1.39	0.958
No. of hospitalizations	4 (0–11)	3 (0–10)	0.355
Newly diagnosed patients	35 (36.1)	26 (24.8)	0.080
Chemotherapy line administered within the period			0.231
First line chemotherapy	77 (79.4)	68 (64.8)	
First and second line chemotherapy	2 (2.1)	4 (3.8)	
Second line chemotherapy	10 (10.3)	19 (18.1)	
Second and third line chemotherapy	1 (1.0)	3 (2.9)	
More than third line chemotherapy	7 (7.2)	11 (10.5)	
Lymphoma subtype			0.592
Hodgkin lymphoma	8 (8.2)	8 (7.6)	
Diffuse large B-cell lymphoma	49 (50.5)	49 (46.7)	
Follicular lymphoma	12 (17.1)	18 (17.1)	
Marginal zone lymphoma	5 (5.2)	6 (5.7)	
Other B-cell lymphomas	7 (7.2)	13 (12·4)	
T-cell lymphoma	16 (16.5)	11 (10.5)	
Disease stage			0.411
Limited (stages I–II)	30 (30.9)	27 (25.7)	
Advanced (stages III–IV)	67 (69.1)	78 (74.3)	
Extranodal involvement	57 (58.8)	68 (64.8)	0.380
Bone marrow involvement	16 (16.5)	30 (28.6)	0.041
LDH above the normal limit	55 (56.7)	63 (60.0)	0.635
ECOG performance status score			0.936
0–1	95 (97.9)	103 (98.1)	
2–4	2 (2.1)	2 (1.9)	
IPI score			0.276
< 3	60 (61.9)	57 (54.3)	
≥ 3	37 (38.1)	48 (45.7)	
Chemotherapy including rituximab	63 (64.9)	72 (68.6)	0.586
COVID-19 test, number	-	3 (0–7)	-
COVID-19 test			
0	-	13 (12.4)	-
1–2	-	32 (30.5)	-
≥ 3	-	60 (57.1)	-

Values are presented as median (range) or number (%).
LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; COVID-19, coronavirus disease 2019.

Table 3. Baseline characteristics of patients with multiple myeloma

Baseline characteristic	Group 1 (2019) (n = 91)	Group 2 (2020) (n = 83)	*p* value
Age, yr	68 (42–89)	69 (42–87)	0.909
Sex ratio, male:female	1.17	1.31	0.713
No. of hospitalizations	3 (1–5)	3 (1–5)	0.197
Newly diagnosed patients	15 (16.5)	9 (10.8)	0.281
Chemotherapy line administered within the period			0.369
First line chemotherapy	39 (42.9)	35 (42.2)	
First and second line chemotherapy	1 (1.1)	3 (3.6)	
Second line chemotherapy	26 (28.6)	15 (18.1)	
Second and third line chemotherapy	1 (1.1)	1 (1.2)	
More than third line chemotherapy	24 (26.4)	29 (34.9)	
Monoclonal protein			0.601
IgG	50 (54.9)	46 (55.4)	
IgA	21 (23.1)	24 (28.9)	
IgM or IgD or IgE	3 (3.3)	1 (1.2)	
Light chain disease	17 (18.7)	12 (14.5)	
International Stage System			0.065
I	26 (28.6)	16 (19.3)	
II	19 (20.9)	30 (36.1)	
III	46 (50.5)	37 (44.6)	
Chemotherapy including bortezomib	34 (37.4)	28 (33.7)	0.618
Chemotherapy including carfilzomib	25 (27.5)	23 (27.7)	0.972
Chemotherapy including thalidomide	10 (11.0)	8 (9.6)	0.770
Chemotherapy including lenalidomide	39 (42.9)	40 (48.2)	0.480
Chemotherapy including pomalidomide	4 (4.4)	11 (13.3)	0.038
COVID-19 tests	-	3 (0–8)	-
COVID-19 test			
0	-	15 (18.1)	-
1–2	-	16 (19.3)	-
≥ 3	-	52 (62.7)	-

Values are presented as median (range) or number (%).
Ig, immunoglobulin; COVID-19, coronavirus disease 2019.

There was no difference between the groups in the median number of inpatients and outpatients per month during each period (group 1, 158 patients [range, 156 to 161], group 2, 166.5 [range, 148 to171], $p = 0.343$; and group 1, 1,049 patients [range, 1,035 to 1,098], group 2, 1,176.5 patients [range, 1,045 to 1,324], $p = 0.114$, respectively).

In patients diagnosed with lymphoma, there was no difference between the two groups in terms of age, sex, lymphoma subtype, disease stage, extranodal involvement, lactate dehydrogenase levels, Eastern Cooperative Oncology Group performance status score, International Prognostic Index score, and the proportion of patients receiving rituximab during chemotherapy. However, the rate of bone marrow involvement was higher in group 2 than in group 1 (group 1, 16/97 patients, 16.5%; group 2, 30/105 patients, 28.6%; $p = 0.041$).

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In patients with multiple myeloma, the proportion of patients receiving pomalidomide during chemotherapy was higher in group 2 than in group 1 (group 1, 4/91 patients, 4.4%; group 2, 11/83 patients, 13.3%; $p = 0.038$). However, there was no difference between the two groups in terms of age, sex, type of multiple myeloma, International Stage System values, and the proportion of patients receiving bortezomib, carfilzomib, thalidomide, or lenalidomide during chemotherapy.

Treatment outcomes and treatment-related adverse events

Among patients with lymphoma, 91 patients in group 1 (83.5%) and 91 patients in group 2 (86.7%) underwent response evaluation within the corresponding periods, and 54 patients in group 1 (55.7%) and 59 patients in group 2 (56.2%) achieved complete remission (Table 4). The 90% CIs for the estimate of the difference were within the equivalence margin (± 15%). In addition, the incidence of neutropenia (group 1, 62/97 patients, 63.9%; group 2, 68/105 patients, 64.8%), incidence of delays in chemotherapy (group 1, 8/97 patients, 8.2%; group 2, 8/105 patients, 7.6%), and number of deaths during chemotherapy (group 1, 9/97 patients, 9.3%; group 2, 4/105 patients, 3.8%) were similar between the two groups. Although the equivalence of the incidence of neutropenic fever was inconclusive, there was no difference between the two groups in the duration of neutropenia or neutropenic fever during chemotherapy (group 1, 2.4 [range, 1.0 to 23.0] vs. group 2, 2.4 [range, 1.0 to 45.0], $p = 0.803$; group 1, 4.0 [range, 1.0 to 15.0] vs. group 2, 4.3 [range, 2.0 to 11.0], $p = 0.585$, respectively). In group 1, the causes of delayed chemotherapy were as follows: infection (four cases: catheter-related bloodstream infection [CRBSI], intra-abdominal infection, candidemia, and neutropenic fever), cytopenia (two cases), and deterioration of the general condition (two cases). In group 2, the causes of delayed chemotherapy were as follows: infection (six cases: three cases of neutropenic fever, one case each of bacteremia, herpes zoster, and fungal arthritis), drug rash caused by chemotherapy (one case), and deterioration of the general condition (one case). In group 1, the causes of death were as follows: infection (five cases: two cases of neutropenic fever, two cases of pneumonia, and

Table 4. Treatment outcomes in patients with lymphoma

Treatment outcome	Group 1 (2019) (n = 97)	Group 2 (2020) (n = 105)
CR rate	54 (55.7)	59 (56.2)
Difference estimate, %	−0.5	
90% CI, %	−12.1 to 11.1	
Incidence of neutropenia	62 (63.9)	68 (64.8)
Difference estimate, %	0.8	
90% CI, %	−10.4 to 12.0	
Incidence of neutropenic fever	27 (27.8)	22 (21.0)
Difference estimate, %	−6.9	
90% CI, %	−16.9 to 3.2	
Incidence of delays in chemotherapy	8 (8.2)	8 (7.6)
Difference estimate, %	−0.6	
90% CI, %	−6.9 to 5.7	
Deaths within the study period	9 (9.3)	4 (3.8)
Difference estimate, %	−5.5	
90% CI, %	−11.3 to 0.3	

Values are presented as number (%).
CR, complete remission; CI, confidence interval.

Table 5. Treatment outcomes in patients with multiple myeloma

Treatment outcome	Group 1 (2019) (n = 91)	Group 2 (2020) (n = 83)
CR or VGPR rate	47 (51.6)	43 (42.9)
Difference estimate, %	−0.2	
90% CI, %	−12.8 to 12.5	
Incidence of neutropenia	32 (35.2)	31 (37.3)
Difference estimate, %	2.2	
90% CI, %	−9.9 to 14.3	
Incidence of neutropenic fever	9 (9.9)	10 (12.0)
Difference estimate, %	2.2	
90% CI, %	−5.7 to 10.0	
Incidence of delays in chemotherapy	9 (9.9)	12 (14.5)
Difference estimate, %	4.6	
90% CI, %	−3.6 to 12.8	
Deaths within the study period	4 (4.4)	4 (4.8)
Difference estimate, %	0.4	
90% CI, %	−4.9 to 5.7	

Values are presented as number (%).
CR, complete remission; VGPR, very good partial response; CI, confidence interval.

one case of bacteremia), bleeding at the cancer site (one case), tumor lysis syndrome (one case), and progression of lymphoma (two cases). In group 2, the cause of death was infection (four cases: two cases of pneumonia, and one case each of CRBSI and neutropenic fever).

In patients with multiple myeloma, 88 patients in group 1 (96.7%) and 82 patients in group 2 (98.8%) underwent response evaluation within the corresponding period, and 47 patients in group 1 (51.6%) and 43 patients in group 2 (42.9%) achieved complete remission or very good partial response (Table 5). The 90% CIs for the estimate of the difference were within the equivalence margin (± 15%). In addition, the incidence of neutropenia (group 1, 32/91 patients, 35.2%; group 2, 31/83 patients, 37.3%), incidence of neutropenic fever (group 1, 9/91 patients, 9.9%; group 2, 10/83 patients, 12.0%), incidence of delays in chemotherapy (group 1, 9/91 patients, 9.9%; group 2, 12/83 patients, 14.5%), and number of deaths during chemotherapy (group 1, 4/91 patients, 4.4%; group 2, 4/83 patients, 4.8%) were similar between the two groups. There were no differences between the two groups in the incidence and duration of neutropenia or neutropenic fever during chemotherapy (group 1, 1.3 [range, 1.0 to 29.0] vs. group 2, 1.3 [range, 1.0 to 22.0], p = 0.931; group 1, 2.0 [range, 1.0 to 3.0] vs. group 2, 2.8 [range, 1.0 to 5.5], p = 0.497, respectively). In group 1, the causes of delayed chemotherapy were as follows: infection (four cases: two cases of pneumonia, one case of urinary tract infection [UTI], and one case of infection of unknown origin) and deterioration of the general condition (five cases). In group 2, the causes of delayed chemotherapy were as follows: infection (five cases: three cases of pneumonia, one case of UTI, and one case of invasive aspergillosis) and deterioration of the general condition (four cases). In group 1, the causes of death were as follows: progression of multiple myeloma (two cases), intra-abdominal infection (one case), and underlying lung disease (one case). In group 2, the causes of death were progression of multiple myeloma (two cases) and infection (two cases: one case of UTI and one case of pneumonia).

There were no positive results for COVID-19 tests conducted according to the countermeasures implemented during the study period.

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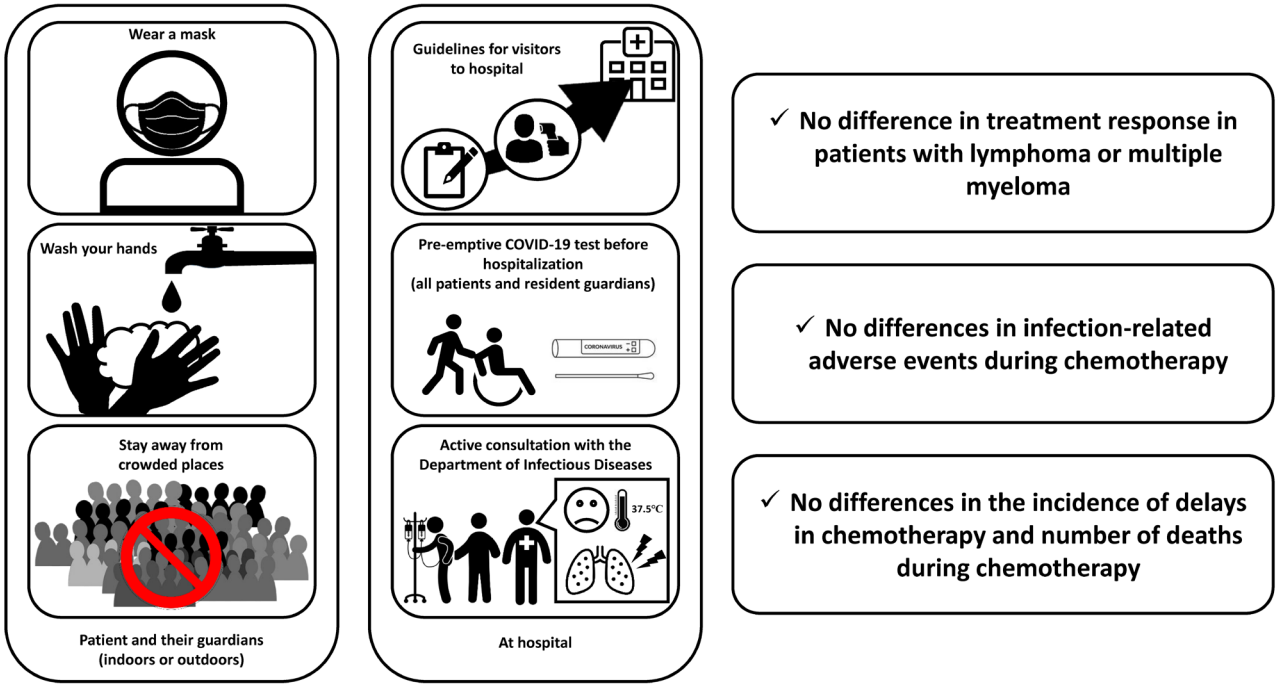

Figure 1. Countermeasures to the coronavirus disease 2019 (COVID-19) pandemic and the results of this study.

DISCUSSION

The population density in Seoul, South Korea, was 15,964 per km^2, and the cumulative number of confirmed cases and deaths related to COVID-19 were 19,363 and 182, respectively, as of January 1, 2021. Although the total number of confirmed COVID-19 cases was relatively small compared with those of other countries, this study was conducted in a situation where the risk of transmission of COVID-19 was expected to be high due to the high population density. In this study, no difference in treatment response, incidence and duration of neutropenia or neutropenic fever, delays in chemotherapy, and deaths during chemotherapy were observed between the control (group 1) and study groups (group 2) of patients with lymphoma or multiple myeloma who were hospitalized repeatedly and received outpatient treatment (Table 1 [26], Fig. 1). In addition, during the study period, none of the patients tested positive for COVID-19, and there were no deaths from COVID-19.

Direct infection via expelled droplets and indirect infection via contact with virus-contaminated surfaces or objects are considered the main routes of transmission of SARS-CoV-2 [1,29]. Droplet transmission occurs when virus-laden droplets from an infected person are expelled during sneezing, coughing, or talking [30]. Exposure to an infected person at a distance of < 2 m for > 15 minutes increases the risk of droplet transmission, and in the case of symptomatic patients, droplet transmission can occur in a shorter time period [31]. In addition, expelled droplets can contaminate surrounding surfaces or objects. When these contaminated surfaces or objects are touched by another person who subsequently touches their eyes, nose, or mouth with their hands before washing them, SARS-CoV-2 infection can develop. The simplest ways to prevent droplet transmission of SARS-CoV-2 are to avoid visiting crowded places, to maintain social distancing, and to wear a mask covering the nose and mouth. In addition, to prevent indirect infection via contact with a virus-contaminated surface or object, it is recommended to refrain from touching your eyes, nose, or mouth with your hands and to wash your hands with soap under running water for at least 20 seconds [32].

The question remains, how should hospitals respond to situations such as the COVID-19 pandemic? For ter-

tiary hospitals, guidance is needed to maintain the safety of patients already receiving treatment, along with appropriate responses to patients with COVID-19. In addition, countermeasures to minimize the depletion of the hospital workforce by ensuring safety are needed. Wearing a mask and washing hands are the most basic requirements for all patients, guardians, and hospital workers in hospitals. Based on data from the European Centers for Disease Control and Prevention, wearing a mask and handwashing resulted in significantly lower mortality and infection rates than did social distancing and handwashing [33]. Following countermeasures implemented in hospitals in Taiwan, establishing quarantine stations at the hospital entrance, screening for COVID-19-related risk factors and the presence of fever in all hospital visitors, and conducting training on wearing masks and handwashing may also be effective countermeasures to prevent hospital-acquired SARS-CoV-2 infection [34,35]. In this study, in addition to the standard countermeasures mentioned above, COVID-19 testing was performed in all patients requiring hospitalization and in their resident guardians, and hospitalization was only permitted once a negative result was obtained. Once admitted, leaving the premises was prohibited, and access to lounges or restaurants in the hospital was restricted. With the implementation of these countermeasures, there was no difference in treatment outcomes between patients with lymphoma or multiple myeloma who received chemotherapy before the COVID-19 pandemic and those who received chemotherapy during the COVID-19 pandemic. In addition, none of the patients tested positive for COVID-19, and there were no deaths from COVID-19 during the study period. To the best of our knowledge, there have been no studies on the treatment outcomes of patients with lymphoma or multiple myeloma who received chemotherapy in the social and medical context of the COVID-19 pandemic. This study may also be meaningful in that it presents countermeasures in an objective manner and offers learning that may be applied clinically should a similar situation occur post-COVID-19.

This study has some limitations. First, this was a retrospective study with a relatively small number of patients; thus, there were limitations intrinsic to the study design. Second, the analysis was performed using data from two tertiary hospitals. Additional studies from a wider variety of institutions and circumstances are needed to determine the appropriateness and effect of the countermeasures presented in this study. Third, the strategy presented in this study was limited in that COVID-19 testing was only routinely conducted in patients who required hospitalization and their resident guardians; however, outpatients, short-term visitors, and hospital workers were selectively tested according to their risk of exposure to COVID-19. In 50% to 80% of patients with COVID-19, there are no symptoms, and the transmission of COVID-19 can occur before symptoms develop [36-38], or even in the absence of symptoms [39-42]. If the population density, disease prevalence, or transmission rate is higher than that in this study, the countermeasures for asymptomatic patients should be modified. Finally, no positive COVID-19 results or deaths were reported among the enrolled patients with lymphoma or multiple myeloma in this study. This may be because the number of newly diagnosed patients with COVID-19 in Seoul was maintained at a level of < 500 per day, most likely due to the active COVID-19 quarantine measures implemented by the South Korean government. It may also be due to the countermeasures implemented by the hospital. However, conclusions on the effectiveness of the countermeasures that were implemented cannot be drawn from this study alone, and more studies in a variety of contexts are required to fully evaluate their efficacy and impact on treatment outcomes for patients with diseases other than COVID-19, particularly malignancies.

In conclusion, patients with lymphoma or multiple myeloma could receive chemotherapy during the COVID-19 pandemic without an adverse effect on treatment outcomes, and without infection-related adverse events, when appropriate countermeasures to COVID-19 were implemented. However, further studies are needed to determine the extent to which countermeasures can be applied, considering variations in population density, the prevalence and transmission rate of infectious diseases, and the characteristics of each institution. In addition, data on countermeasures to COVID-19 and the effects of these countermeasures should continue to be analyzed and shared to maintain optimal treatment outcomes for patients with existing diseases other than COVID-19 in the context of a shifting pandemic.

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KEY MESSAGE

1. Patients with lymphoma or multiple myeloma could receive chemotherapy during the coronavirus disease 2019 (COVID-19) pandemic without an adverse effect on treatment outcomes, and without infection-related adverse events, when appropriate countermeasures to COVID-19 were implemented.
2. Data on countermeasures to COVID-19 and the effects of these countermeasures should continue to be analyzed and shared to maintain optimal treatment outcomes for patients with existing diseases other than COVID-19 in the context of a shifting pandemic.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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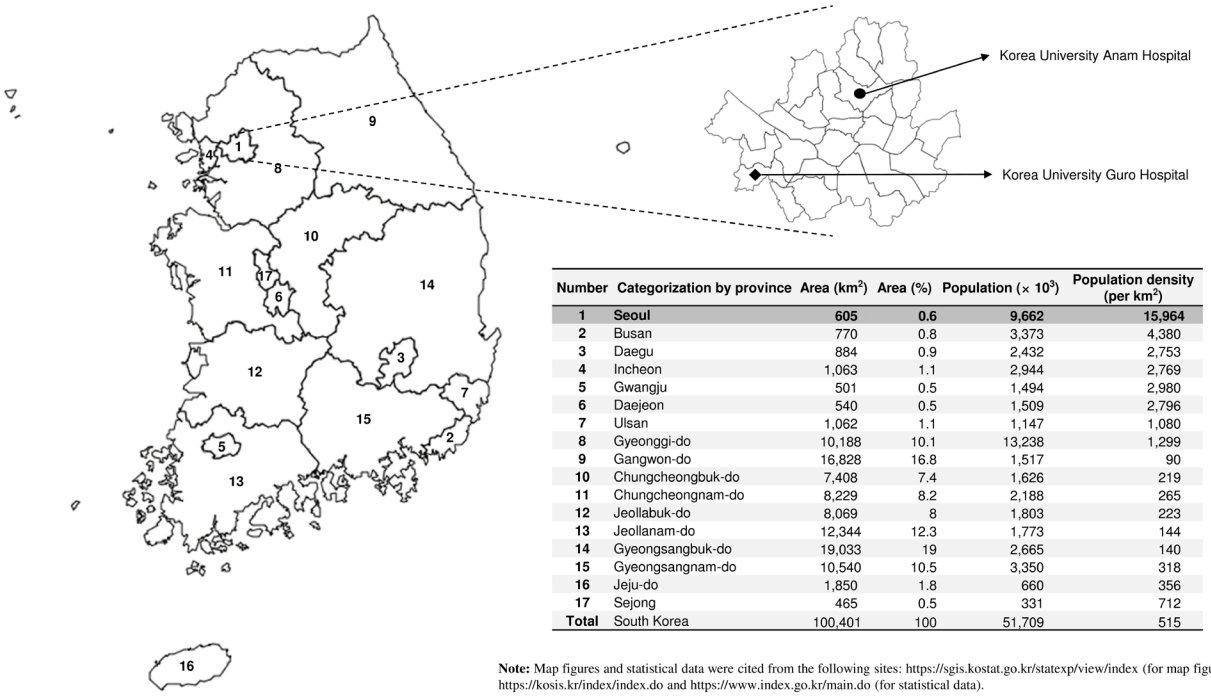
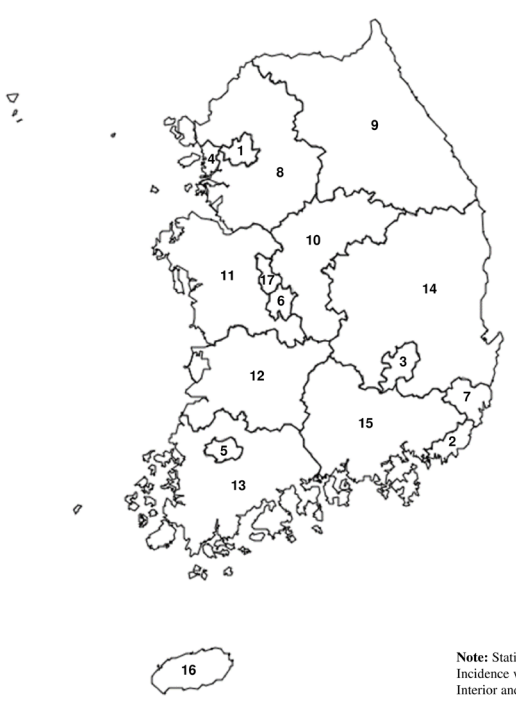
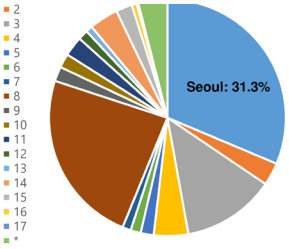


Number	Categorization by province	Area (km^2)	Area (%)	Population ($\times 10^3$)	Population density (per km^2)
1	**Seoul**	**605**	**0.6**	**9,662**	**15,964**
2	Busan	770	0.8	3,373	4,380
3	Daegu	884	0.9	2,432	2,753
4	Incheon	1,063	1.1	2,944	2,769
5	Gwangju	501	0.5	1,494	2,980
6	Daejeon	540	0.5	1,509	2,796
7	Ulsan	1,062	1.1	1,147	1,080
8	Gyeonggi-do	10,188	10.1	13,238	1,299
9	Gangwon-do	16,828	16.8	1,517	90
10	Chungcheongbuk-do	7,408	7.4	1,626	219
11	Chungcheongnam-do	8,229	8.2	2,188	265
12	Jeollabuk-do	8,069	8	1,803	223
13	Jeollanam-do	12,344	12.3	1,773	144
14	Gyeongsangbuk-do	19,033	19	2,665	140
15	Gyeongsangnam-do	10,540	10.5	3,350	318
16	Jeju-do	1,850	1.8	660	356
17	Sejong	465	0.5	331	712
Total	South Korea	100,401	100	51,709	515

Note: Map figures and statistical data were cited from the following sites: https://sgis.kostat.go.kr/statexp/view/index (for map figures); https://kosis.kr/index/index.do and https://www.index.go.kr/main.do (for statistical data).

Supplementary Figure 1. Population and population density of South Korea [23-25].





Number	Categorization by province	Confirmed cases	Quarantined	Released from quarantine	Deceased	Incidence
1	**Seoul**	**19,363**	**8,394**	**10,787**	**182**	**644.4**
2	Busan	1,925	505	1,370	50	17.59
3	Daegu	7,844	349	7,294	201	294.85
4	Incheon	2,904	725	2,150	29	35.93
5	Gwangju	1,098	228	864	6	35.42
6	Daejeon	856	160	689	7	30.12
7	Ulsan	716	233	457	26	14.38
8	Gyeonggi-do	14,735	3,929	10,535	271	42.62
9	Gangwon-do	1,237	318	906	13	19.21
10	Chungcheongbuk-do	1,185	532	629	24	12.19
11	Chungcheongnam-do	1,668	465	1,180	23	29.92
12	Jeollabuk-do	845	190	644	11	9.19
13	Jeollanam-do	566	86	475	5	10.19
14	Gyeongsangbuk-do	2,448	482	1,904	62	59.76
15	Gyeongsangnam-do	1,360	315	1,041	4	10.20
16	Jeju-do	421	202	219	0	8.95
17	Sejong	150	20	129	1	23.95
*****	Lazaretto	2,448	766	1,680	2	—
Total	South Korea	61,769	17,899	42,953	917	52.62

Note: Statistical data (as of 00 on 1.1.2021) were cited from the following sites: http://ncov.mohw.go.kr/; https://kosis.kr/covid/covid_index.do. Incidence was calculated as the number of confirmed cases every 100,000 people (Source: Census Data as of January 2020, Ministry of the Interior and Safety).

Supplementary Figure 2. The cumulative number of confirmed coronavirus disease 2019 (COVID-19) cases in South Korea [26-28].

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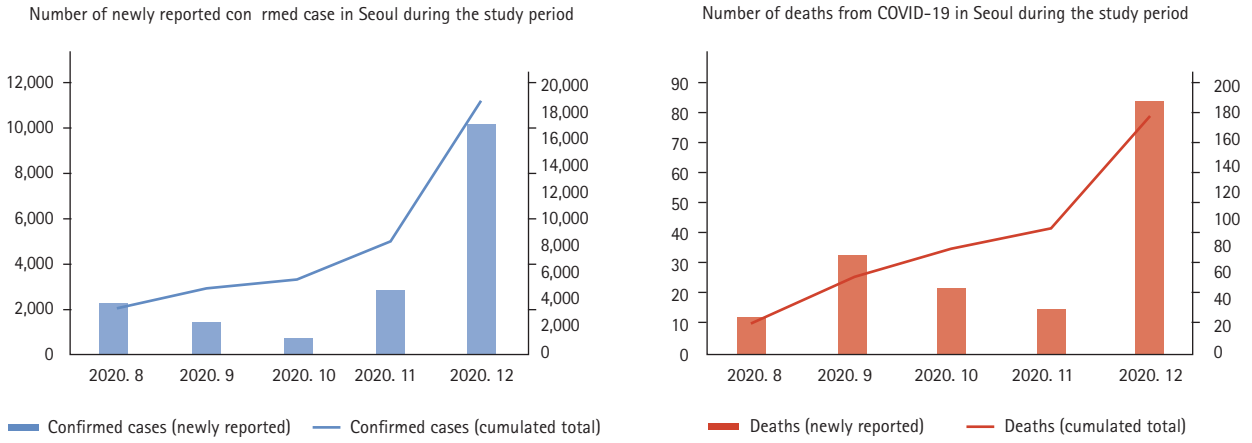

Supplementary Figure 3. The number of newly reported coronavirus disease 2019 (COVID-19) cases and number of deaths from COVID-19 during the study period in Seoul [26,27].