ANTICANCER RESEARCH *41*: 2193-2195 (2021)
doi:10.21873/anticanres.14994

A Retrospective Analysis of Perioperative Chemotherapy and Coronavirus Disease in Patients With Breast Cancer

KAZUMI HAYASHI[1], MIHO TAMURA[1], EIJIRO NAGASAKI[1], YUKIKO YOSHII[2], TAKAYUKI ISHIGAKI[2], TAKASHI KAZAMA[2], MAKIKO KAMIO[2], HIROKO NOGI[2], YASUO TORIUMI[2], HIROSHI TAKEYAMA[2] and SHINGO YANO[1]

[1]*Department of Clinical Oncology and Hematology, The Jikei University School of Medicine, Tokyo, Japan;*
[2]*Department of Breast and Endocrine Surgery, The Jikei University School of Medicine, Tokyo, Japan*

Abstract. *Background/Aim: Since January 2020, coronavirus disease (COVID-19) cases have been confirmed in Japan, and the number of patients with COVID-19 has been increasing. Two emergency declarations have been made previously and one is currently in effect. Based on our experience of a situation that could affect cancer treatment, this study retrospectively examined the correlation between perioperative anticancer therapy and COVID-19 incidence in patients with breast cancer. Patients and Methods: Patients who underwent perioperative anticancer therapy for breast cancer at our hospital from February 2020 to February 2021 were included in this study. The presence or absence of COVID-19, timing of anticancer drug initiation, and clinical data were collected. Results: No cases of COVID-19 were diagnosed in patients receiving perioperative anticancer therapy at our hospital. Conclusion: Regimen modification, active use of supportive care, and patient lifestyle were factors reducing the incidence of COVID-19.*

Since January 2020, patients with coronavirus disease (COVID-19) have been confirmed in Japan, and the number of patients has been increasing (1). There have been three epidemics of COVID-19 in Japan, with the first wave peaking on April 11, 2020 with 720 new cases; the second wave peaking on August 7 with 1,605 cases; and the third wave peaking on January 8, 2021 with 7,882 cases (3). In addition, a state of emergency has been declared twice so far, the first from April 7, 2020 to May 25, 2020 and the second on January 7, 2021, and we experienced situations that could affect cancer treatment. Furthermore, the European Society for Medical Oncology reported that anticancer drug therapy may suppress the immune system, and thus, regimen changes or treatment postponement may be considered (2). The epidemic began in earnest in Japan around February 2020, and the number of new patients with breast cancer at our hospital decreased. In addition, the number of new patients with breast cancer at our hospital decreased owing to concerns about the immunocompromised state caused by anticancer drug treatment, and thus, we began to consider postponing perioperative anticancer treatment or changing the regimen. However, the correlation between anticancer drug therapy and COVID-19 in patients with breast cancer remains unclear.

In our hospital, there were no cases of COVID-19 among patients receiving anticancer drugs in the outpatient clinic. In this study, we retrospectively analyzed the perioperative anticancer drug treatment of patients over the past year.

Correspondence to: Kazumi Hayashi, MD, Ph.D., Department of Clinical Oncology and Hematology, The Jikei University School of Medicine, 3-25-8 Nishi-shinnbashi, Minato-ku, Tokyo 105-8471, Japan. Tel: +81 334331111, Fax: +81 334362171, e-mail: kz.hayashi@gmai.com

Key Words: Covid-19, breast cancer, chemotherapy.

Patients and Methods

Patients who received perioperative anticancer drugs for breast cancer at our hospital from February 2020 to January 2021 were included in the study, and the following data were collected: age, stage of breast cancer, regimen, whether the regimen was changed, whether the start of anticancer drugs was postponed, number of days postponed (more than 1 month because our hospital allows the start of anticancer drugs within 1 month of the initial diagnosis), presence of symptoms suggestive of COVID-19, use of granulocyte colony-stimulating factor (G-CSF), work status, residence, and lifestyle. In this study, patients with a positive nucleic acid amplification test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were diagnosed as having COVID-19.

The protocol for anticancer drugs implemented at our hospital is as follows: Adriamycin and cyclophosphamide (AC) every 3 weeks (doxorubicin 60 mg/m^2 IV on day 1, cyclophosphamide 600 mg/m^2 IV day 1, repeated every 21 days for four cycles); AC followed by docetaxel (DTX) every 3 weeks (doxorubicin 60 mg/m^2 IV on day 1, cyclophosphamide 600 mg/m^2 IV day 1, repeated every 21 days for four cycles, followed by docetaxel 75 mg/m^2 IV on day 1, repeated

every 21 days for four cycles); AC followed by weekly paclitaxel (doxorubicin 60 mg/m^2 IV day 1, cyclophosphamide 600 mg/m^2 IV day 1, repeated every 21 days for four cycles, followed by paclitaxel 80 mg/m^2 IV infusion weekly for 12 weeks); AC followed by docetaxel+trastuzumab+pertuzumab (doxorubicin 60 mg/m^2 IV day 1, cyclophosphamide 600 mg/m^2 IV day 1, repeated every 21 days for four cycles, followed by pertuzumab 840 mg IV day 1 then followed by 420 mg IV, trastuzumab 8 mg/kg IV day 1 and 6 mg/kg IV, and docetaxel 75 mg/m^2 IV day 1, repeated every 21 days for four cycles, followed by trastuzumab 6 mg/kg IV, pertuzumab 420 mg IV day 1, repeated every 21 days); AC followed by docetaxel+trastuzumab (doxorubicin 60 mg/m^2 IV day 1, cyclophosphamide 600 mg/m^2 IV day 1, repeated every 21 days for four cycles, followed by trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV docetaxel 75 mg/m^2 IV day 1, repeated every 21 days for four cycles, followed by trastuzumab 6 mg/kg IV, repeated every 21 days); Paclitaxel+trastuzumab (paclitaxel 80 mg/m^2 IV weekly for 12 weeks, trastuzumab 4 mg/kg IV administered with the first dose of paclitaxel, followed by trastuzumab 6 mg/kg every 21 days may be used after the completion of paclitaxel); Docetaxel+trastuzumab (docetaxel 75 mg/m^2 IV day 1, repeated every 21 days for four cycles, with trastuzumab 8 mg/kg IV week 1, followed by trastuzumab 6 mg/kg IV every 21 days to complete 1 year of trastuzumab therapy); trastuzumab (trastuzumab 8 mg/kg IV week 1, followed by trastuzumab 6 mg/kg IV every 21 days to complete 1 year of trastuzumab therapy); CMF (cyclophosphamide 600 mg/m^2 IV day 1, methotrexate 40 mg/m^2 IV days 1 and 8, 5-fluorouracil 600 mg/m^2 IV days 1 and 8, repeated every 28 days for six cycles). Data collection and analysis was performed using Microsoft Excel.

Results

Patient characteristics. In total, 43 patients were treated with perioperative anticancer drugs (Table I). The patients were all female, and the median age was 55 years. Thirteen patients were aged 49 years or younger. Fourteen patients were aged 50-59 years. Seven patients were aged 60-69 years, and nine patients were aged 70 years or older. The stage of breast cancer was stage I in 10 patients, stage II in 26 patients, and stage III in seven patients. Sixteen and 27 patients received neoadjuvant and adjuvant therapies, respectively. The number of patients living in Tokyo was 30, and 9 lived outside Tokyo. No cases of COVID-19 were diagnosed in patients receiving perioperative anticancer therapy at our hospital.

Treatment. Among the patients, two received AC, 13 received AC followed by docetaxel (AC followed by DTX), 12 received AC followed by paclitaxel (AC followed by PTX), eight received AC followed by docetaxel+trastuzumab+pertuzumab (AC followed by DTX+Tras+Per), three received AC followed by docetaxel+trastuzumab (AC followed by DTX+Tras), two received docetaxel+trastuzumab (DTX+Tras), one received paclitaxel+trastuzumab (PTX+Tras), one received trastuzumab (Tras), and one received CMF. Nine patients were currently employed.

Table I. *Patient characteristics*.

Patient characteristics	n	%
Age		
0-49	13	30.2
50-59	14	32.6
60-69	7	16.3
70-	9	20.9
Stage		
I	10	23.3
II	26	60.5
III	7	16.3s
Types of chemotherapy		
Neoadjuvant	16	37.2
Adjuvant	27	62.8
Chemotherapy regimen		
AC	2	4.7
AC followed by DTX	13	30.2
AC followed by PTX	12	27.9
AC followed by DTX+Tras+Per	8	18.6
AC followed by DTX+Tras	3	7
DTX+Tras	2	4.7
PTX+Tras	1	2.3
Tras	1	2.3
CMF	1	2.3
Place of residence		
Tokyo	30	69.8
Outside Tokyo	13	30.2
Working in a company		
Yes	9	20.9
No	34	79.1

CMF: Cyclophosphamide, methotrexate, 5-fluorouracil; DTX: docetaxel.

The regimen was changed from dose-dense AC to AC therapy in one patient and from paclitaxel to docetaxel in three patients. In addition, two patients delayed treatment initiation owing to the COVID-19 outbreak and both patients postponed their treatment for 2 months.

Primary G-CSF support. G-CSF preparations were used as primary prophylaxis to avoid immunocompromise in 32/38 (84%) patients who received AC therapy and in 22/26 (84%) patients who received docetaxel therapy.

Start date of anticancer therapy and number of patients with COVID-19. The date of initiation of anticancer therapy and the number of patients treated are shown in Figure 1. The number of patients treated with perioperative anticancer therapy decreased from January 2020 to March 2020 owing to a decreased number of new patients, but the number gradually increased thereafter.

From February 2020 to January 2021, none of the patients who received anticancer therapy for breast cancer at our hospital were infected with COVID-19. None of the patients

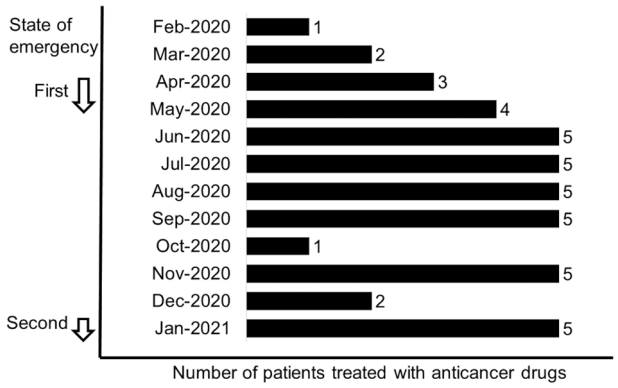

Figure 1. *The month in which the anticancer drug was started and the number of patients treated. Two emergency declarations were made in Japan, and the timing of the first and second declarations are indicated by the arrows.*

had symptoms suggestive of COVID-19, such as fever, cough, or abnormal taste.

What patients did to prevent COVID-19. Almost all patients wore masks when they went out of their homes or visited their doctor. In addition, almost all patients were actively washing their hands and disinfecting their hands with alcohol.

Discussion

In May 2020, the SARS-CoV-2 polymerase chain reaction (PCR) Center was established at our hospital to enable conducting PCR tests for SARS-CoV-2 at our own facilities. Until then, it was difficult to reliably diagnose COVID-19 because PCR could not be performed at our facility. Epidemiological studies to date have reported fever, cough, sore throat, malaise, and myalgia. The median incubation period was approximately 5 days, and 97.5% of the patients developed symptoms within 11.5 days after infection (4). Therefore, in this survey, we also investigated symptoms suggestive of COVID-19. As a result, none of the patients had symptoms suggestive of COVID-19.

Because of the absence of perioperative COVID-19 in our hospital, anticancer therapy was not postponed in the second and third waves. As a result, no patients with COVID-19 received perioperative anticancer treatment throughout the year.

From a retrospective perspective, the anticancer drug regimen was changed from paclitaxel to docetaxel to reduce the number of visits to the hospital, and dose-dense therapy that is highly immunosuppressive was not used. The use of G-CSF preparations as much as possible is thought to have reduced coronary incidence. Another factor could have been the effect of lifestyle. Wearing masks, thorough hand washing and disinfection, avoiding crowded places, and not having much contact with other people, as the percentage of people working on-site for their employment was small, may have contributed to the decrease in the incidence rate. Anthracyclines such as Adriamycin, have antiviral effects against herpes viruses, but there are few reports of antiviral effects of anticancer agents. Therefore, we think it is unlikely that the anticancer drugs used in this study had antiviral effects (5).

This study suggests that perioperative anticancer drugs may be safely administered even in COVID-19 outbreak areas and periods if patients take thorough precautions to prevent COVID-19 and medical professionals select regimens that reduce the number of hospital visits and actively provide supportive care.

Conflicts of Interest

The Authors state that they have no conflicts of interest in relation to this study.

Authors' Contributions

Conception and design: Kazumi Hayashi. Analysis and interpretation of data: Miho Tamura, Eijiro Nagasaki, Yukiko Yoshii, Takayuki Ishigaki, Takashi Kazama, Makiko Kamio, Hiroko Nogi, Yasuo Toriumi, Hiroshi Takeyama, and Shingo Yano. Writing, review, and revision of the manuscript: Kazumi Hayashi.

References

1 Furuse Y, Ko YK, Saito M, Shobugawa Y, Jindai K, Saito T, Nishiura H, Sunagawa T, Suzuki M, Oshitani H and National Task Force for COVID-19 Outbreak in Japan.: Epidemiology of COVID-19 outbreak in Japan, from January-March 2020. Jpn J Infect Dis *73(5)*: 391-393, 2020. PMID: 32350228. DOI: 10.7883/yoken.JJID.2020.271

2 Management and Treatment Adapted Recommendations in the Covid-19 Era: Breast cancer, European Society for Medical Oncology(ESMO). Available at: https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic [Last accessed on February 3, 2021]

3 Amengual O and Atsumi T: COVID-19 pandemic in Japan. Rheumatol Int *41(1)*: 1-5, 2021. PMID: 33205224. DOI: 10.1007/s00296-020-04744-9

4 Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG and Lessler J: The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med *172(9)*: 577-582, 2020. PMID: 32150748. DOI: 10.7326/M20-0504

5 Cohen A, Harley EH and Rees KR: Antiviral effect of daunomycin. Nature *222(5188)*: 36-38, 1969. PMID: 4304749. DOI: 10.1038/222036a0

Received February 11, 2021
Revised February 20, 2021
Accepted February 22, 2021