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Research Article

Impact of Early Chemotherapy Resumption on the Outcome after *Staphylococcus aureus* Bacteremia in Patients with Solid Tumors: A Retrospective Study in a Single Tertiary Cancer Center in Japan

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Objective. *Staphylococcus aureus* bacteremia (SAB) in patients with solid tumors poses a dilemma between infection control and cancer treatment. We aimed to explore whether early resumption of chemotherapy yielded unfavorable outcomes in oncologic patients with SAB. *Methods*. We retrospectively reviewed patients who received chemotherapy within 90 days of SAB onset from 2011 to 2020. We divided patients who resumed chemotherapy into two groups by the median time from the negative blood culture to the chemotherapy resumption. We investigated the association with treatment failure, which included recurrence after completion of SAB treatment, relapse during antibiotics therapy, 90-day all-cause mortality after initiation of antibiotics, and 30-day all-cause mortality after the resumption of chemotherapy. *Results*. Among the 78 eligible patients, 36 patients resumed chemotherapy. The median interval to the chemotherapy resumption was 17.5 days. Two patients in the early resumption group and one in the late resumption group died within 90 days after initiating antibiotics. One patient in the early resumption group experienced SAB recurrence. None of the patients experienced SAB relapse or died within 30 days of resuming chemotherapy. *Conclusion*. Early resumption of chemotherapy may not be directly associated with unfavorable outcomes in oncological patients with SAB under appropriate infection management.

1. Introduction

The incidence rate of *Staphylococcus aureus* bacteremia (SAB) is about 20 to 50 cases per 100,000 population per year [1]. SAB is a common adverse event in patients with solid tumors that often require interruption of planned cancer treatments, including systemic chemotherapy [2]. Generally, multiprofessional support is essential for SAB treatment. Conditions such as early consultation with infectious disease (ID) specialists [3–7] and confirmation of negative blood cultures [8–11] are associated with a favorable SAB prognosis. The vulnerability of oncologic patients to SAB is driven by immunosuppression due to cancer or chemotherapy and the vascular access devices used, including central venous catheters or peripherally inserted central catheters [12]. The recommended duration of antibiotic treatment for SAB in immunosuppressed patients is more than four weeks [8]. A dilemma arises between infection control and cancer treatment in the medical oncology setting. The timing of chemotherapy resumption is one of the most frequently asked questions. However, there are no guidelines regarding when to resume chemotherapy for SAB

patients with solid tumors [10, 13, 14]. We aimed to explore whether early resumption of chemotherapy yielded an unfavorable outcome for SAB in oncologic patients.

2. Methods

2.1. Study Design. This retrospective study was conducted at Shizuoka Cancer Center, a tertiary care facility in Japan. Clinical data were obtained from the electronic medical charts of patients who met the inclusion and exclusion criteria and were hospitalized in any clinical division of Shizuoka Cancer Center from January 1, 2011, to December 31, 2020. The inclusion criteria were as follows: (1) age >18 years, (2) bacteriologically proven SAB, (3) pathologically proven solid tumor, and (4) having received antineoplastic chemotherapy within 90 days before the onset of SAB. Exclusion criteria were as follows: (1) no follow-up data after SAB (e.g., transfer to another hospital), (2) polymicrobial bacteremia, (3) no documentation of negative blood culture after SAB, (4) hormonal therapy as antineoplastic chemotherapy, or (5) hematologic malignancy. A preprint has previously been published [15].

2.2. Data Collection. Two investigators obtained clinical information from the electronic medical records and extracted the data. The variables included age, sex, Eastern Cooperative Oncology Group performance status (PS), cancer histology and stage, type of chemotherapy, presence of vascular access devices, control of infection sources, ID consultation, methicillin-resistant *Staphylococcus aureus* (MRSA), Pitt bacteremia score, serum albumin, and mortality. In addition, we collected data, including the number of days from negative blood culture to chemotherapy resumption and the number of deaths within 30 days after chemotherapy resumption. The Institutional Ethics Review Board approved the study protocol of Shizuoka Cancer Center (approval number: J2020-167-2021-1-2). The requirement for informed consent was waived because of the retrospective nature of this study.

2.3. Definitions. SAB was defined as at least one blood culture positive for *S. aureus* with clinically apparent signs and symptoms of sepsis [16], with a documentation of sepsis. Catheter-related bloodstream infection (CRBSI) was defined as a primary bloodstream infection in patients with a central venous or peripheral catheter that was present for at least 48 hours before the onset of bacteremia and had no identifiable source of infection outside the catheter [17]. The severity of bacteremia was based on the Pitt bacteremia score [18]. The duration of antibiotic therapy was defined as the number of days patients received susceptible antibiotics based on bacteriological tests for the patient's isolate [19]. Treatment failure included either (1) recurrence, defined as a return of SAB after completing an antibiotic course with negative blood cultures; (2) relapse, defined as a positive blood culture for *S. aureus* ≥ 48 hours after a negative blood culture during an antibiotic course; (3) 90-day all-cause mortality after initiation of susceptible antibiotics; and (4) 30-day all-cause mortality after the resumption of chemotherapy [20, 21]. We defined the early and late resumption groups by the median time from the negative blood culture date to the resumption of chemotherapy.

2.4. Microbiological Identification. Microbiological identification was confirmed using the MicroScan WalkAway 40 plus System (Beckman Coulter, California, USA) until November 6, 2016, and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) using a MALDI Biotyper (Bruker Daltonics, Bremen, Germany) from November 7, 2016. We confirmed antibiotic susceptibility using the MicroScan WalkAway 40 plus System until October 14, 2018, and the DxM 1096 MicroScan WalkAway System (Beckman Coulter, California, USA) from October 15, 2018. The data were interpreted according to the recommendations and criteria of the Clinical and Laboratory Standards Institute.

2.5. Statistical Analysis. We used the Mann–Whitney *U* test to compare differences in continuous variables and Fisher's exact test to compare the proportions of categorical variables between the groups. All tests were two-sided, and statistical significance was defined as a p value <0.05. Statistical analyses were performed using R version 4.1.2 (The R Foundation, Vienna, Austria).

3. Results

A total of 269 consecutive patients with SAB were assessed for eligibility between January 2011 and December 2020. We excluded 191 patients: 101 without chemotherapy before SAB, 48 without confirmation of negative blood culture, and 24 with polymicrobial bacteremia. Finally, 78 patients who underwent systemic chemotherapy before the onset of SAB were included. Among the eligible patients, 36 resumed chemotherapy after SAB, and 42 did not (Figure 1). Table 1 shows the baseline characteristics of the patients who underwent chemotherapy before SAB. The median age of the 78 eligible patients was 69 years (range, 28–83 years), and 67% were men. Forty-two (54%) and 36 (46%) patients had PS scores of 0-1 and 2–4, respectively. Forty-three patients (55%) had gastrointestinal cancer, including colorectal cancer ($n = 20$), gastric cancer ($n = 7$), pancreatic cancer ($n = 7$), esophageal cancer ($n = 4$), hepatocellular carcinoma ($n = 2$), duodenal cancer ($n = 1$), neuroendocrine cancer ($n = 1$), and maxillary cancer ($n = 1$). Thoracic cancers included nonsmall cell lung cancer ($n = 7$) and small cell lung cancer ($n = 2$). The remaining 26 patients had breast cancer ($n = 7$), oropharyngeal cancer ($n = 5$), bladder cancer ($n = 2$), cancers of unknown primary origin ($n = 2$), prostate cancer ($n = 2$), renal pelvic cancer ($n = 1$), testicular cancer ($n = 1$), glioma ($n = 1$), glioblastoma ($n = 1$), rhabdomyosarcoma ($n = 1$), Ewing sarcoma ($n = 1$), cervical cancer ($n = 1$), and melanoma ($n = 1$). Most patients had metastatic disease ($n = 65$, 83%) and received first-line chemotherapy ($n = 40$, 51%) at the onset of SAB. Chemotherapeutic regimens included cytotoxic ($n = 70$, 90%) or targeted agents ($n = 8$,

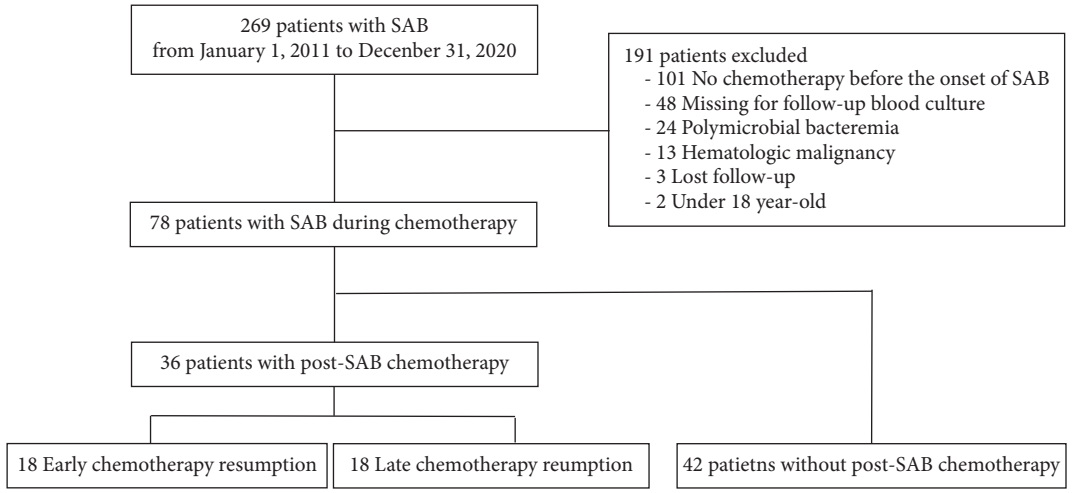

Figure 1: Study flowchart. The cut-off time between early and late resumption groups was used as the median time for chemotherapy resumption (17.5 days). SAB, *Staphylococcus aureus* bacteremia.

Table 1: Characteristics of the patients with SAB during chemotherapy.

Characteristics	Total ($n = 78$)	Chemotherapy after SAB		P value*
		Resumption ($n = 36$)	Nonresumption ($n = 42$)	
Age, median (range)	69.0 (28–83)	63.5 (28–78)	71.0 (41–83)	<0.001
Sex (male), *n* (%)	52 (67)	20 (56)	32 (76)	0.091
ECOG-PS, *n* (%)				<0.001
0-1	42 (54)	30 (83)	12 (29)	
2–4	36 (46)	6 (17)	30 (71)	
Cancer type, *n* (%)				
Gastrointestinal cancers†	43 (55)	23 (64)	20 (48)	0.176
Thoracic cancers‡	9 (12)	2 (5)	7 (17)	0.166
Breast cancers	7 (9)	5 (14)	2 (5)	0.239
Others§	19 (24)	6 (17)	13 (31)	0.189
Cancer status, *n* (%)				1.000
Metastatic	65 (83)	30 (83)	35 (83)	
Nonmetastatic	13 (17)	6 (17)	7 (17)	
Chemotherapy line, median (range)	1 (1–11)	1 (1–11)	2 (1–6)	0.634
Chemotherapy, *n* (%)				
Cytotoxic agents	70 (90)	35 (97)	35 (83)	0.063
Targeted agents	8 (10)	1 (3)	7 (17)	<0.001
Source of infection, *n* (%)				
CRBSI	51 (65)	27 (75)	24 (57)	0.152
Skin and soft tissue	6 (8)	4 (12)	2 (5)	0.406
Pneumonia	6 (8)	1 (3)	5 (12)	0.209
Unknown origin	10 (13)	2 (5)	8 (19)	0.097
Others	5 (6)	2 (5)	3 (7)	1.000
MRSA, *n* (%)	14 (18)	5 (14)	9 (21)	0.555
ID consultation, *n* (%)	73 (94)	36 (100)	37 (88)	0.058
Pitt bacteremia score, median (range)	0 (0–9)	1 (0–4)	0 (0–9)	0.972
Serum albumin, median (range)	2.8 (1.4–5.0)	3.2 (1.7–5.0)	2.7 (1.4–3.9)	0.008

*P value for comparison between chemotherapy resumption and nonresumption. †Colorectal cancer, gastric cancer, pancreatic cancer, esophageal cancer, hepatocellular carcinoma, duodenal cancer, neuroendocrine cancer, and maxillary cancer. ‡Nonsmall cell lung cancer and small cell lung cancer. §Oropharyngeal cancer, bladder cancer, cancers of unknown primary origin, prostate cancer, renal pelvic cancer, testicular cancer, glioma, glioblastoma, rhabdomyosarcoma, Ewing sarcoma, cervical cancer, and melanoma. ECOG, Eastern Cooperative Oncology Group; PS, performance status; SAB, *Staphylococcus aureus* bacteremia; CRBSI, catheter-related bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus*; ID, infectious disease.

10%). None of the patients in this study received hormone or immunotherapy. Fifty-one patients (65%) had CRBSI, 47 (92%) of which were from central venous catheters, and four (8%) were from peripheral catheters. Central venous catheters were removed within three days of positive blood culture in 35 patients (74%) with central venous catheter infection. Other sources of infection included skin and soft tissue infections ($n = 6$, 8%), pneumonia ($n = 6$, 8%), infections of unknown origin ($n = 10$, 13%), osteomyelitis ($n = 2$, 2.6%), device-related infections except for CRBSI

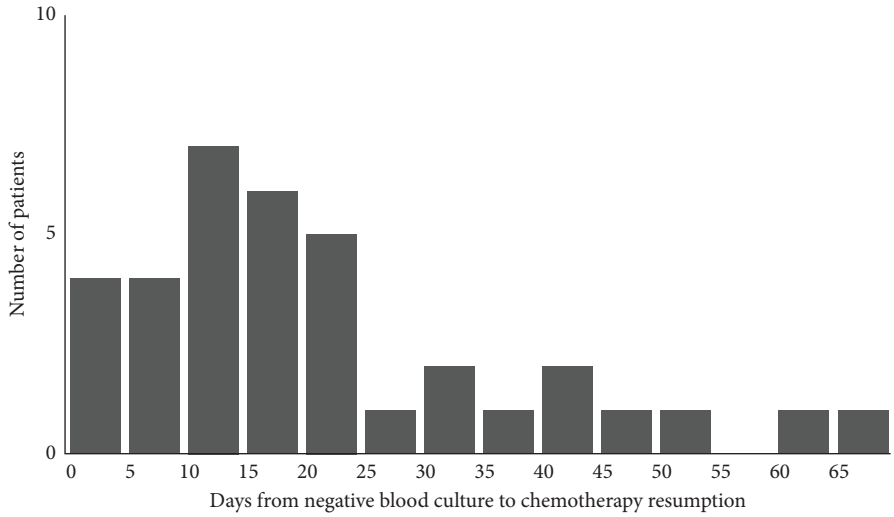

Figure 2: Histogram of time to resumption of chemotherapy after negative blood culture. Day 0 was defined as the day when a negative blood culture was taken.

($n = 1$, 1.3%), thrombophlebitis ($n = 1$, 1.3%), and suppurative parotitis ($n = 1$, 1.3%). Methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in 14 patients (18%). All patients with SAB were admitted to the hospital, and 73 (94%) were referred to the ID team, who managed antibiotics according to age, body weight, renal function, allergy status, and antibiotic susceptibilities. The median Pitt bacteremia score was 0 (0–9) points, and four (5%) had a score ≥ 4 points. Empirical antibiotics included vancomycin ($n = 71$, 91%), cefazolin ($n = 2$, 3%), and ampicillin-sulbactam ($n = 2$, 3%) at the time of the first positive blood culture report. Antibiotics were modified in 52 patients based on the susceptibility of confirmed *S. aureus* and modified regimens included cefazolin ($n = 38$, 49%), ceftriaxone ($n = 7$, 9%), and cefepime ($n = 7$, 9%). The median duration of antibiotic administration was 33.5 days (range, 5–363 days).

Table 1 shows the baseline characteristics of patients with and without resumption of chemotherapy. Patients who did not resume chemotherapy were older (71.0 vs. 63.5 years, $p < 0.001$), and had poorer PS (71% vs. 17% for 2–4, $p < 0.001$) and lower serum albumin (2.7 vs. 3.2 mg/dL, $p = 0.008$) than those who resumed chemotherapies after SAB. There were no statistical differences between the groups regarding sex, cancer type, cancer status, chemotherapy treatment line, CRBSI, and MRSA. ID consultations tended to be fewer in the nonresumption group, but the difference was not statistically significant (100% vs. 88%, $p = 0.058$).

Figure 2 shows the duration distribution from the date of negative blood culture to the date of chemotherapy resumption among patients in the resumption group ($n = 36$). The median duration was 17.5 days (range, 0–69 days). Two patients resumed chemotherapy ≥ 2 months after obtaining a negative blood culture: one patient developed SAB-related thrombophlebitis and osteomyelitis requiring 41 days of intravenous antibiotics, and the other had persistent bacteremia requiring 53 days of intravenous antibiotics. We further classified the 36 patients into two groups based on the median days to resuming chemotherapy (approximately 17 to 18 days), which were defined as the early ($n = 18$) and late ($n = 18$) resumption groups. The median days to chemotherapy resumption in each group were 13 (range, 0–16 days) and 25.5 days (range, 19–69 days), respectively. Baseline characteristics of the two groups are shown in Table 2, and no significant differences were found except for age (58.0 vs. 67.0; $p = 0.048$). Filgrastim/peg-filgrastim was used for neutropenia in 2 of 2 patients in the early resumption group and 2 of 3 patients in the late resumption group. All these patients were not associated with treatment failures. All 38 patients performed an echocardiogram, and only one patient was diagnosed with infectious endocarditis. However, it was not associated with treatment failure. In terms of chemotherapy, only two patients in the early resumption group changed cytotoxic agents to targeted agents after the onset of SAB. They fully recovered without the event of treatment failures. Regarding SAB treatment failures (Table 3), one patient (2.8%) experienced SAB recurrence, and three out of the 36 who resumed chemotherapy (8.3%) died within 90 days after initiating antibiotics toward susceptible microorganisms. There was no SAB relapse or death within 30 days after the resumption of chemotherapy. One patient in the early resumption group developed SAB and underwent reinsertion of the central venous port after resolution of the previous SAB episode with antibiotics toward susceptible microorganisms and had SAB again because of central venous port infection 89 days after completing a course of antistaphylococcal antibiotics for the first episode. The 90-day all-cause mortality rates in the early and late resumption groups were 2/18 (11.1%) and 1/18 (5.6%), respectively. Two patients in the early resumption group died 22 and 43 days after the completion of antibiotics toward susceptible microorganisms, respectively. One patient in the late resumption group died 21 days after the first SAB episode. These deaths were attributed to the underlying cancer progression without an apparent

Table 2: Characteristics of the patients among early and late resumption of chemotherapy.

Characteristics	Early or late chemotherapy resumption		P value
	Early ≦17.5 days ($n = 18$)	Late >17.5 days ($n = 18$)	
Age, median (range)	58.0 (28–71)	67.0 (44–78)	0.048
Sex (male), n (%)	10 (56)	10 (56)	1.000
ECOG-PS, n (%)			0.658
0-1	14 (78)	16 (89)	
2–4	4 (22)	2 (11)	
Cancer type, n (%)			
Gastrointestinal cancers	11 (61)	12 (67)	1.000
Thoracic cancers	2 (11)	0 (0)	0.243
Breast cancers	4 (22)	1 (6)	0.338
Others	1 (6)	5 (27)	0.177
Cancer status, n (%)			0.177
Metastatic	17 (94)	13 (72)	
Nonmetastatic	1 (6)	5 (28)	
Chemotherapy line, median (range)	1 (1–11)	1.5 (1–5)	0.505
Chemotherapy			1.000
Cytotoxic agents	18 (100)	17 (94)	
Targeted agents	0 (0)	1 (6)	
Source of infection, n (%)			
CRBSI	16 (88)	11 (61)	0.121
Skin and soft tissue	1 (6)	3 (16)	0.353
Pneumonia	0 (0)	1 (6)	1.000
Unknown origin	1 (6)	1 (6)	1.000
Others	0 (0)	2 (11)	0.486
MRSA, n (%)	2 (11)	3 (16)	1.000
ID consultation, n (%)	18 (100)	18 (100)	1.000
Pitt bacteremia score, median (range)	0 (0–4)	1 (0–3)	0.453
Serum albumin, median (range)	3.25 (2.0–5.0)	2.9 (1.7–4.2)	0.346
Days from negative blood culture to chemotherapy resumption, median (range)	13 (0–16)	25.5 (19–69)	<0.001

ECOG, Eastern Cooperative Oncology Group; PS, performance status; SAB, *Staphylococcus aureus* bacteremia; CRBSI, catheter-related bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus*; ID, infectious disease.

Table 3: Treatment failures of *S. aureus* bacteremia after chemotherapy resumption.

Treatment failure	Early or late chemotherapy resumption	
	Early ≦17.5 days ($n = 18$)	Late >17.5 days ($n = 18$)
Relapse of bacteremia*	0 (0)	0 (0)
Recurrence of bacteremia†	1 (5.6)	0 (0)
90-day mortality after initiating antibiotics	2 (11.1)	1 (5.6)
30-day mortality after chemotherapy resumption	0 (0)	0 (0)

Data are given as the number (%) of patients. *Relapse was defined as a positive blood culture for *S. aureus* ≥48 hours after a negative blood culture during antibiotic treatment. †Recurrence was defined as a positive blood culture for *S. aureus* after the completion of antibiotic treatment.

relationship with SAB. With regard to the relevance of CRBSI, treatment failures occurred in 3 of 16 patients in the early resumption group with CRBSI and in 1 of 11 patients in the late resumption group with CRBSI.

4. Discussion

This is the first study to assess the impact of chemotherapy resumption on the outcome of SAB in patients with solid tumors. First, we showed that early resumption of chemotherapy was not associated with unfavorable outcomes in patients with appropriate antistaphylococcal antibiotic treatment and confirmed negative blood cultures. Second, we characterized oncological SAB in contrast to non-oncological SAB in terms of baseline characteristics, etiology, and treatment outcomes. These findings may help understand oncological SAB and promote future studies.

Early resumption of chemotherapy is desirable for the treatment of many primary diseases. Our study showed that most oncologists opted to resume chemotherapy based on the necessity of controlling cancer in patients with metastatic disease receiving palliative chemotherapy. The treatment failure rate was low in both the early- and late-resumption groups, which may be attributed to appropriate infection management. Previous studies have identified favorable prognostic factors for SAB management, including undetected infective carditis [22, 23], appropriate antibiotic choices, duration of antibiotic treatment [11],

documentation of negative blood cultures, and ID consultation. In our study, all patients who resumed chemotherapy were referred to the ID physicians who managed antibiotics, screened for complications, and monitored blood cultures. In cases of treatment failures, one case of recurrence in the early resumption group occurred 89 days after completing the initial SAB treatment. However, a new infection due to the insertion of the CV port after the completion of the previous SAB episode was considered. The 90-day mortality rate was 8% (three patients) in this study, and all deaths occurred after completing the initial SAB treatment. The deaths were not associated with antineoplastic chemotherapy or SAB episodes and were deemed related to the progression of primary diseases. Although the incidence of treatment failure in our study was rare, the early resumption of chemotherapy may not be directly associated with unfavorable outcomes in well-managed patients with SAB. Furthermore, most chemotherapies were first-line treatments in the early resumption group; therefore, early resumption of chemotherapy during first-line treatment may provide a potentially valuable oncologic benefit to patients with solid tumors.

To clarify the characteristics of solid tumor patients with SAB, we compared the differences between the resumption and nonresumption groups, as well as the differences between our oncological SAB and previously reported SAB in the general population. The proportion of patients with good PS (0-1) in the resumption group was 83% compared to 29% in the nonresumption group, which may primarily affect the physician's decision to resume chemotherapy. In addition, the use of molecular-targeted treatment was less common in the resumption group, which may be another feature of oncological SAB. Regarding the source of infection, CRBSI was the most common (65%), and skin and soft tissue infections were the least common (8%). However, SAB in the general population is characterized by a significant difference in major origins with CRBSIs (18.8–37.6%) and skin and soft tissue infections (14.8–25.7%) [9, 19, 24, 25]. In our study, the 90-day mortality rate was 8% (three patients), which was lower than that in the existing report of approximately 30% in the general population and 36% in patients with malignancy [9, 24–27]. This discrepancy may be partially attributed to the general condition of patients at the time of SAB onset. Rieg et al. showed that the 90-day mortality rate was 31.5%, but severe sepsis and septic shock accounted for approximately 45% of patients, influencing the high mortality rate [25]. Another reason for the low mortality in our study may be the high proportion of CRBSI as a source of infection because many patients had central venous lines for chemotherapy in this study, and source control was relatively easy owing to catheter removal. Although all treatment failures in this study occurred in cases of CRBSI, we could not say any association between CRBSI and treatment failures, since two-thirds of the cases were CRBSI cases and the number of cases itself is small. These findings suggest that early resumption of chemotherapy may be feasible without increasing the chance of treatment failure in patients with good PS at the onset of SAB and a well-controlled source of infection.

This study had several limitations. First, it was a retrospective cohort study, and patients did not follow the same treatment protocol, even after ID consultations. Second, this study was possibly underpowered because the number of treatment failures was small owing to the small sample size. Therefore, we could not conclude that there was a statistically significant relationship between treatment failures and early resumption of chemotherapy. Third, patients with hematological malignancies were excluded; thus, the results cannot be generalized to all malignancies. Fourth, we combined the data on multiple solid tumors and antineoplastic chemotherapy agents, which should be considered a possible confounding factor in the analysis. Fifth, this study was conducted in a tertiary care facility specializing in cancer care, with a high rate of ID consultations. Thus, it is not easy to generalize our results to all facilities. However, if patients with SAB are appropriately managed, our results can be generalized to facilities without ID physicians.

In conclusion, treatment failures are generally rare regardless of the timing of chemotherapy resumption in SAB cases in patients with solid tumors with appropriate management of infection if the PS is low and the source of infection is well controlled. However, our study may imply the possibility that early resumption is not necessarily associated with unfavorable outcomes. Early resumption is beneficial for patients for whom chemotherapy, including palliative purposes, is an inevitable part of their treatment. Further research is required to validate these hypotheses leading to a better outcome with multiprofessional cancer care.

Data Availability

The data supporting these study's findings are available upon request from the corresponding author.

Disclosure

This article was submitted as a preprint in the website https://www.researchsquare.com/article/rs-1596811/v1.

Conflicts of Interest

Tateaki Naito received a lecture fee from ONO Pharmaceutical Co., Ltd., and Helsinn Healthcare SA and research funding from Otsuka Pharmaceutical Co., Ltd. The remaining authors declare that they have no conflicts of interest.

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