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Effects of molecular targeting agents and immune-checkpoint inhibitors in patients with advanced cancer who are near the end of life

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Abstract

Background. In recent years, the use of both molecular targeting agents (MTAs) and immune-checkpoint inhibitors (ICIs) tend to occupy important positions in systemic anticancer therapy (SACT). The objective of this study is to describe the predictors of SACT include both MTAs and ICIs near the end of life (EOL) and the effect on EOL care in patients with advanced cancer.

Methods. We analyzed all patients who died of advanced cancer from August 2016 to August 2019, and we analyzed the survival time of patients who underwent anticancer agents excluded due to the loss of information about the last administration of SACT. The primary endpoint of this study was to identify predictors during the last administration of SACT near EOL.

Results. In a multivariate analysis, the Eastern Cooperative Oncology Group performance status (ECOG-PS) (ORs 33.781) was significantly related factors within 14 days of death from the last administration of SACT. Age (ORs 0.412), ECOG-PS (ORs 11.533), primary cancer site of upper GI cancers (ORs 2.205), the number of comorbidities (ORs 0.207), MTAs (ORs 3.139), and ICIs (ORs 3.592) were significantly related factors within 30 days of death. The median survival time (MST) of patients with PS 3–4 was 29 days, while that of patients with both PS 0–2 was 76 days. The prevalence rate of delirium with MTAs was 17.5%, which was significantly lower than that of patients without it (31.8%). The prevalence rate of the mean dose of opioids in patients with ICIs was 97.9 mg/day, which was significantly higher than that of patients without it (44.9 mg/day).

Conclusions. Age, ECOG-PS, primary cancer site, the number of comorbidities, MTAs, and ICIs use were significant associated with SACT near EOL. Information on these factors may aid clinical decision making in referral to palliative care institutes.

Introduction

Systemic anticancer therapy (SACT), which includes cytotoxic agents (CTAs), molecular targeting agents (MTAs), and immune-checkpoint inhibitors (ICIs), improves the prognosis of patients with advanced cancer. However, aggressive therapy has proven to be disadvantageous for patients with advanced cancer who are near the end of life (EOL).

Earle reported that aggressive SACT near EOL resulted in an increased number of emergency department visits, hospitalizations, and admissions to intensive care units during the final month of life in patients with advanced cancer (Earle et al., 2004). According to this report, SACT near EOL was tentatively defined as the last administration of therapy to patients within 14 or 30 days prior to death. Kao reported that younger age, the cancer type, and tumor chemosensitivity were predictive factors for performing SACT near EOL during the final week before death (Kao et al., 2009). Petra reported that patients with breast, hematological, and gynecological cancers were 2.5 times more likely to undergo SACT near EOL than other cancer patients (Petra et al., 2015). Hiramoto reported that the Glasgow Prognostic Scale and the Eastern Cooperative Oncology Group performance status (ECOG-PS) were significant prognostic factors in patients with advanced cancer in the EOL stage (Hiramoto et al., 2019). In these studies, rates of the last administration of SACT within 14 and 30 days prior to death were reported as 3.0–11.6% and 6.3–18.8%, respectively (Earle et al., 2004; Barbera et al., 2006; Braga et al., 2007; Hashimoto et al., 2009; Kao et al., 2009; Näppä et al., 2011; Hui et al., 2013; Hanny et al., 2014; Petra et al., 2015; Maltoni et al., 2016; Hikmat et al., 2019; Hiramoto et al., 2019).

Recently, the use of both MTAs and ICIs has occupied important positions in SACT. However, there are few reports on the effects of using MTAs and ICIs near EOL in patients

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with advanced cancer in SACT (Hui et al., 2013; Tsai et al., 2018; Glisch et al., 2020), while other reports focused only on CTAs (Earle et al., 2004; Barbera et al., 2006; Braga et al., 2007; Hashimoto et al., 2009; Kao et al., 2009; Näppä et al., 2011; Hanny et al., 2014; Petra et al., 2015; Maltoni et al., 2016; Hikmat et al., 2019; Hiramoto et al., 2019; Glisch et al., 2020).

SACT is used to improve the quality of life (QOL) of patients with advanced cancer; however, previous studies have reported that it could not improve the QOL of patients with a poor performance status (Prigerson et al., 2015). Moreover, SACT near EOL has become an indicator of poor quality of cancer care. Aggressive treatment near EOL increases the number of hospitalizations in the intensive care unit and delays the palliative care referral (Hikmat et al., 2019). Among patients for whom there was no evidence of clinical value, the American Society of Clinical Oncology expert panel identified chemotherapy use as the most widespread, wasteful, and unnecessary practice in oncology (Schinipper et al., 2012). A better understanding of predictors and the effect on the EOL care would provide valuable information for clinicians, patients, and their families for decision making in referral to palliative care institutes.

Therefore, the objective of this study was to describe the predictors of SACT, including both MTAs and ICIs near EOL, and the effects on EOL care in patients with advanced cancer.

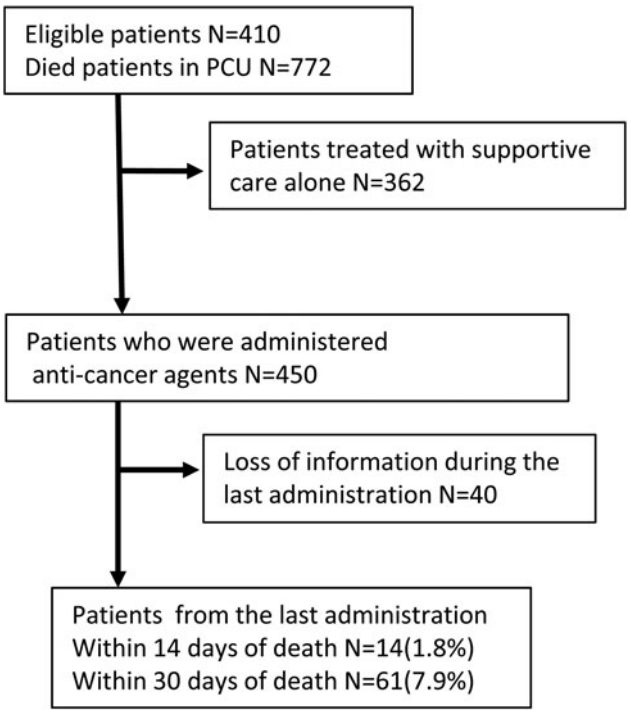

Fig. 1. Patient selection flow.

Methods

Study design and patients

This study was conducted as a retrospective analysis. We analyzed all patients who died of advanced cancer, brain tumors, or advanced hematological malignancies from August 2016 to August 2019 at Mitsubishi Kyoto Hospital. Patients aged 20 years or older and diagnosed with advanced cancer with metastatic and recurrence states were included. We analyzed the survival time of patients who were applied anticancer agents excluded due to the loss of information about the last administration of SACT (Figure 1).

At our department, physicians can provide both oncological treatments such as SACT and specialized palliative care, including the EOL care. We provide services such as SACT and supportive care for cancer patients from their diagnosis to death. We routinely evaluate patients' symptoms, ECOG-PS, and blood test before the SACT administration in the outpatient treatment room. If the patient needs to be hospitalized due to SACT side effects, disease progression, and their EOL, we support them in the palliative care unit or general wards in our hospital.

Endpoints

The primary endpoint of this study was to identify related factors during the last administration of SACT near EOL after dividing the patients into two groups (patients who died within 14 or 30 days after the last administration of SACT and others) and examine differences between them.

Related factors involved data collection during the last administration of SACT near EOL and included information such as age, sex, ECOG-PS, primary cancer site, the number of metastatic sites, the number of comorbidities, and the use of MTAs, ICIs, and CTAs in the last administration. Biliary, pancreatic, esophageal, and gastric cancers were classified as upper gastrointestinal (GI) for the related factor analysis. Data regarding age, sex, primary cancer site, metastatic site, and the number of comorbidities were collected at the time of the first diagnosis in patients with metastatic and recurrent states, and ECOG-PS was applied at the last administration of SACT retrospectively.

For the factor analysis, we used the above factors in a logistic analysis after dividing them into two groups.

The secondary endpoint was to analyze the relationship between EOL symptoms and EOL treatment details. With respect to EOL symptoms, our palliative care physician took care of each patient as a daily clinical practice. Delirium was diagnosed using the confusion assessment method (Inoue et al., 1990). The diagnoses of cancer pain, dyspnea, nausea and vomiting, and fatigue were determined based on clinical findings. The prevalence of distressing symptoms and details of EOL treatments were evaluated during the three days prior to death. We defined continuous deep sedation as the continuous use of sedatives to relieve intolerable and refractory symptoms with a total loss of patient consciousness until death (Morita et al., 2005). The number of opioids administered was recorded in terms of the oral morphine-equivalent dose.

Statistical analysis

Time of the event curves was calculated using the Kaplan–Meier method and compared using log-rank tests. The statistical influence was presented and interpreted based on multiple logistic regression models (ORs) and 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant. All analyses were performed using the R version 3.6.2. for OS X 10.11.

Ethical considerations

This study was conducted in accordance with the ethical requirements of the Declaration of Helsinki and the ethical guidelines for epidemiological research, presented by the Ministry of Health,

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Table 1. Patient background

	All patients ($N = 772$)	Within 30 days of death ($N = 61$)	p-value
Median Age (AVERAGE)	73.0 (72.6)	67 (64.3)	>0.001
Sex			0.927
Male	384	30	
Female	388	31	
Primary cancer site			
Gastro-esophageal	113	13	
Biliary-pancreatic	152	16	
Colorectal	107	7	
Lung	161	13	
Breast	46	4	
Urological and gynecological	80	3	
Hepatocellular carcinoma	31	1	
Others (BT/HMG/HN/Sarcoma)	64	4	
Metastatic site			
Liver	213	20	
Lung	137	5	
Peritoneum	202	25	
Bone	130	10	
Brain	62	6	
Others	138	16	
Total number of Meta sites ≥2	138	22	0.915
Comorbidity			
Cardiac-Renal	146	7	
Respiratory	66	5	
Metabolic disease	96	3	
Mental	68	1	
Liver	39	1	
Cranial Nerve system	58	1	
Others	28	2	
Total number of comorbidities ≥2	115	2	0.021
Chemotherapy			
Yes	450		
No	322		
	Patients who received Chemotherapy $N = 410$	Patients within 30 days of death $N = 61$	p-value
ECOG-PS (3–4) in last administration	19	10	>0.001
Molecular Targeted agents in last administration	57	13	0.123
Molecular Targeted agents use during therapy	151	26	0.372
Immune-checkpoint agents in last administration	44	9	0.333
Immune-checkpoint agents use during therapy	59	12	0.278
Cytotoxic agents = 1 in last administration	214	9	0.183
Cytotoxic agents ≥2 in last administration	79	9	0.297

BT, brain tumor; HNK, head and neck cancer; HMG, hematological malignancy.

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Table 2. Predictors analysis for the last administration of SACT (multi-regulation analysis)

Prognostic factor		Within 14 days of death				Within 30 days of death			
		ORs	95% CIs		*p*-value	ORs	95% CIs		*p*-value
Age	≥70/<70	0.752	0.215	2.631	0.656	0.412	0.230	0.738	0.003
Sex	Male/Female	2.509	0.669	9.408	0.173	0.864	0.488	1.530	0.616
ECOG-PS	3–4/Others	33.781	8.257	138.206	>0.001	11.533	4.082	32.583	>0.001
Primary site	Upper GI/Others	2.755	0.740	10.256	0.131	2.205	1.209	4.024	0.010
Number of Meta sites	≥2/Others	1.924	0.528	7.015	0.322	0.935	0.484	1.806	0.841
Number of Comorbidities	≥2/Others	0.424	0.042	4.332	0.469	0.207	0.045	0.945	0.042
MTAs in last administration	Yes/No	4.065	0.608	27.157	0.148	3.139	1.240	7.943	0.016
ICIs in last administration	Yes/No	2.364	0.336	16.625	0.387	3.592	1.443	8.942	0.006
CTAs in last administration	≥2/Others	1.962	0.412	9.329	0.397	1.722	0.816	3.633	0.154

SACT, systemic anticancer therapy; ORs, odds ratio; CIs, confidential interval; Upper GI, esophageal and gastric, pancreatic and biliary cancer; MTAs, molecular targeting agents; ICIs, immune-checkpoint inhibitors; CTA, cytotoxic agents.

Labour and Welfare of Japan. The hospital institutional review board approved this study.

Results

Patients' background

Among the 772 patients who died at our institute during the study period, 362 received supportive care only, and of the 450 patients who underwent SACT among them, 40 patients were excluded due to the loss of information regarding the last SACT administration. The number of patients who died within 14 and 30 days from the last SACT administration was 14 (1.8%) and 61 (7.9%), respectively (Figure 1). No patients died within three days from the last administration of SACT. The patients' backgrounds are described in Table 1, and details of the last SACT administration are described in the Supplementary Appendix table.

Related factors analysis

In a multivariate analysis, the ECOG-PS (OR 33.781, $p < 0.001$) was a significant predictor for the period within 14 days of death from the last SACT administration. Age (ORs 0.412, $p = 0.003$), ECOG-PS (OR 11.533, $p < 0.001$), primary cancer site for upper GI cancers (OR 2.205, $p = 0.010$), the number of comorbidities (OR 0.207, $p = 0.042$), MTAs (OR 3.139, $p = 0.016$), and ICIs (OR 3.592, $p = 0.006$) were significant predictors within 30 days of death (Table 2). The median survival time (MST) from the last SACT administration to death in patients with ECOG-PS 3–4 was 29 days, while that of patients with both PS 0–2 was 76 days. The MST of patients with upper GI cancers was 76 days, while that of patients with other cancers was 95 days. The MST of patients with MTA was 59 days, while that of patients without MTA was 93 days. The Kaplan–Meier survival curve was stratified by ECOG-PS, primary cancer site (upper GI), and MTAs (Figure 2).

Prevalence of EOL symptoms and details of EOL treatments

The prevalence rate of delirium in EOL patients with MTAs in the last administration of SACT was 17.5%, which was significantly lower than that in patients without MTAs (31.8%). The prevalence rate of the mean opioid dose in patients with ICIs was 97.9 mg/day, which was significantly higher than that in patients without ICIs (44.9 mg/day) (Table 3).

Discussion

In this study, age, ECOG-PS, primary cancer site, the number of comorbidities, MTAs, and ICIs use were significantly associated with SACT near EOL. To the best of our knowledge, this is the first study to analyze the predictors of SACT near EOL and include both MTAs and ICIs.

In young patients, the focus is on the prolongation of life expectancy, and they tend to receive an aggressive treatment compared with elderly patients. Moreover, they hope to continue treatment near EOL and cannot decide to discontinue it, whereas palliative care referral tends to be delayed (Hashimoto et al., 2009; Hikmat et al., 2019). The result that patients with comorbidities had a good prognosis compared with those without seems paradoxical, but considering age factors, patients with comorbidities would likely avoid aggressive treatment from the start of treatment. As a result, elderly patients with comorbidities have a good prognosis near EOL.

SACT is used to improve the QOL of patients with advanced cancer; however, previous studies have reported that it could not improve the QOL of patients with poor performance status (Prigerson et al., 2015). Our study has also suggested that ECOG-PS should be considered as a factor related to SACT near EOL. Thus, an early referral to palliative care should be considered as low scores on the ECOG-PS that indicate poor prognosis.

In general, the overall survival time after the diagnosis of unresectable biliary, pancreatic, esophageal, and gastric cancers is short against SACT, and the malignancy potential is high compared with other cancers (Hiramoto et al., 2018). Moreover, there was a report that the survival time from intervention to death in palliative care facilities was also short (Hiramoto et al., 2016). As the MST from the last administration of SACT to death was brief (76 days), compared with other cancers (95 days), it might be better to rapidly introduce palliative care.

Small molecular agents of the MTAs are commonly used in patients with non-small lung cancer (Inoue et al., 2009). The

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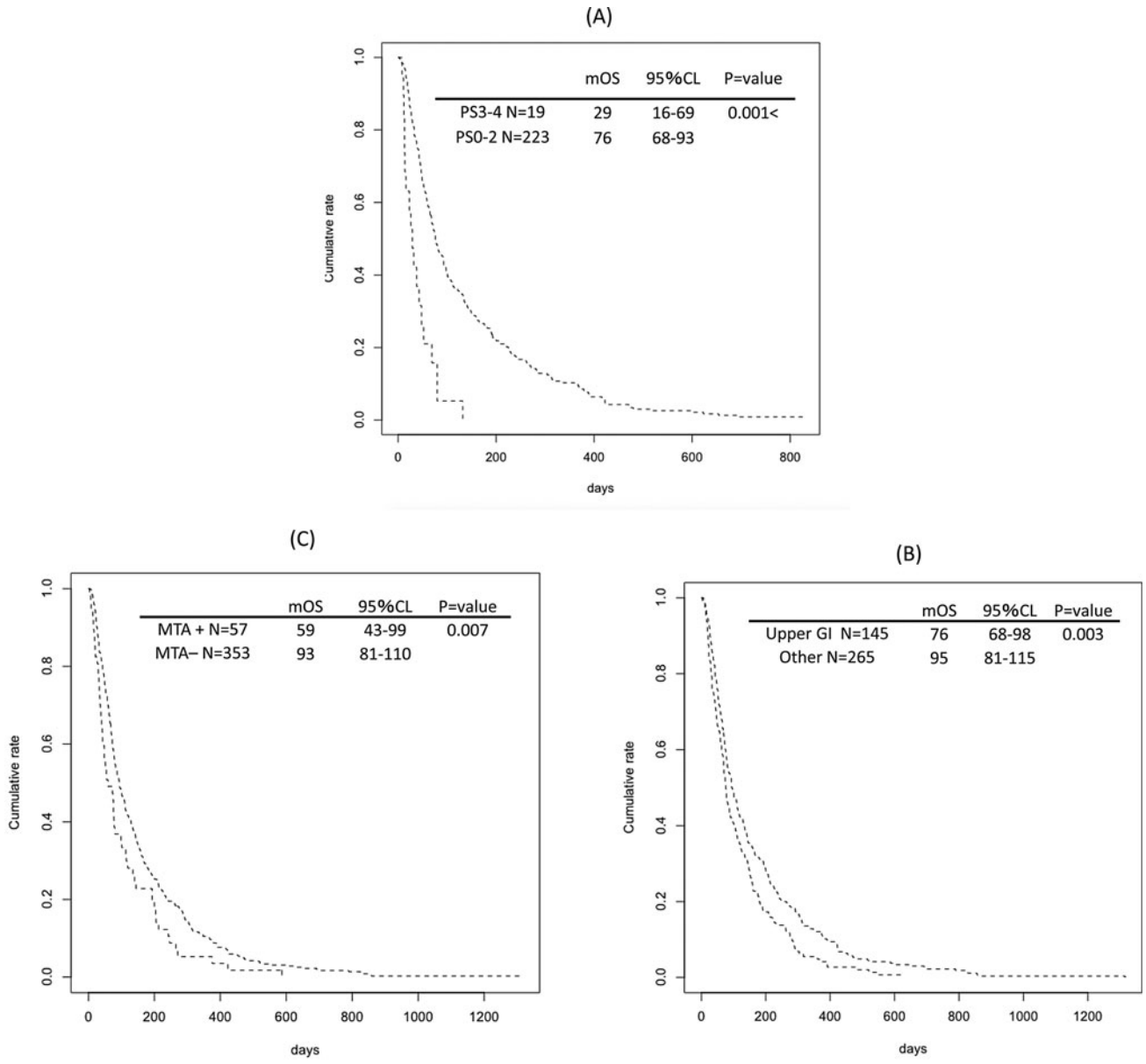

Fig. 2. Survival time from the last administration of SACT for patients stratified by ECOG-PS (a); Primary cancer site (b) and MTAs (c) (Kaplan–Meier survival curve).

Table 3. Relationship between the last administration of SACT, end-of-life symptom and treatment

		Prevalence of end-of-life symptom					Details in end-of-life treatment		
		Delirium	Cancer pain	Dyspnea	Nausea and vomiting	Fatigue	Mean of hydration (L/day)	Continuous deep sedation	Mean opioid dose (mg/day)
MTAs in last administration	Yes *N* = 57	17.5%	28.1%	24.5%	3.5%	12.3%	0.10	21.1%	37.7
	No *N* = 719	31.8%	22.9%	14.8%	7.0%	18.7%	0.09	17.9%	48.9
p-value		0.02	0.38	0.06	0.31	0.22	0.73	0.55	0.32
ICIs in last administration	Yes *N* = 44	41.3%	23.9%	23.9%	2.2%	23.9%	0.09	23.9%	97.9
	No *N* = 729	30.2%	23.3%	15.0%	7.0%	17.9%	0.09	17.7%	44.9
p-value		0.11	0.92	0.11	0.20	0.31	0.92	0.29	0.00

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MTAs of SACT near EOL were correlated with younger age, hematological malignancy, and lung cancer, and they were often used with CTAs in past reports (Hui et al., 2013). Moreover, it has been reported that the use of MTAs near EOL was related to aggressive EOL care, which included multiple emergency department visits, hospitalization exceeding 14 days, admission to intensive care units, the use of intubation and mechanical ventilation, cardiopulmonary resuscitation, and late hospice referrals, and it should be a quality-of-care indicator in patients with non-small lung cancer (Tsai et al., 2018). In our study, there were more patients with small molecular agents (84.2%) than antibodies (15.8%) who used regimens in MTAs monotherapy of SACT for lung and colorectal cancer, and 31 patients used a combination of CTAs.

The ICI use near EOL is associated with a poor performance status, lower hospice enrollment, and death in the hospital (Glisch et al., 2020). As the ICI use near EOL was a significant predictor in our study, attention should be paid to the prolonged use of ICIs for patients with poor Performance Status for the same reasons as for the MTAs. Considering past reports, it is important not to delay referral to a palliative institute such as hospice care.

There have been few reports of associations between EOL symptoms, treatment, and SACT (Hiramoto et al., 2019). ICI neurotoxicity was associated with immune-related adverse events, so the result was paradoxical. We assume that there is a low prevalence of delirium in patients who used ICIs, as it is less intensive, and the fact that fatigue was low suggests a low possibility of delirium. Nausea and vomiting near EOL were less prevalent in patients receiving MTAs because there was less use of CTAs that affected these symptoms. The opioid use between MTAs and ICIs was different, so there may be different biological effects in patients or differences in the pharmacological effects of the opioid metabolism.

This study has several limitations. First, as it was a retrospective study conducted in a single institution in Japan, the findings may be less likely to be generalized; thus, further validation is necessary. Second, MTAs were associated with SACT near EOL. However, it is difficult to know whether it is a trend to prolong the use for patients with poor performance status due to a low burden for patients or affect the prognosis expectancy directly. To solve this problem, a prospective study is necessary to analyze the effects of MTAs near EOL, stratified according to the performance status. Third, the MTAs are divided into two types: small molecules and antibody agents, but it is difficult to analyze these classifications using statistics. Fourth, we only used a small number of ICIs in this study, but the number of ICIs used in the future will gradually increase. Fifth, we cannot analyze the rate of acute hospitalization and hospice admission separately because the institute considered in this study is an integrated palliative care unit and oncology center.

Conclusions

Age, ECOG-PS, primary cancer site, the number of comorbidities, MTAs, and ICIs use were significantly associated with SACT near EOL. Information on these factors may aid clinical decision making in referral to palliative care institutions. In addition, further investigations of SACT with MTAs and ICIs for EOL are required.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S147895152100002X.

Conflict of interest. There are no conflicts of interest to declare.

References

Barbera L, Paszat L and Chartier C (2006) Indicators of poor-quality end-of-life cancer care in Ontario. *Journal of Palliative Care* **22**(1), 12–17.

Braga S, Rute Fonseca AM, Moreira A, *et al.* (2007) The aggressiveness of cancer care in the last three months of life: A retrospective single centre analysis. *Psycho-Oncology* **16**(9), 863–868.

Earle CC, Neville BA, Lndrum MB, *et al.* (2004) Trends in aggressiveness of cancer care near the end of life. *Journal of Clinical Oncology* **22**(2), 315–321.

Glisch C, Hagiwara Y, Lyckholm L, *et al.* (2020) Immune checkpoint inhibitor use near the end of life. *Journal of Palliative Medicine* **23**(7), 977–979.

Hanny A, Sonja H and Georg B (2014) Chemotherapy near the end of life: A retrospective single-center analysis of patients' charts. *BMC Palliative Care* **13**, 26.

Hashimoto K, Yonemori K, Katsumata N, *et al.* (2009) Factors that affect the duration of the interval between the completion of palliative chemotherapy and death. *Oncologist* **14**(7), 752–759.

Hikmat A, Omar S, David H, *et al.* (2019) Intensity of cancer care near the end of life at a tertiary care cancer center in Jordan. *Journal of Pain and Symptom Management* **57**(6), 1106–1113.

Hiramoto S, Maeda I, Morita T, *et al.* (2016) Effect of primary site on the prognosis in patients with advanced-stage cancer in palliative care settings (J-Proval): A multicenter prospective cohort study in Japan. *Journal of Clinical Oncology* **34**(15 suppl), 10025.

Hiramoto S, Kato K, Boku N, *et al.* (2018) A retrospective analysis of 5-fluorouracil plus cisplatin as first line chemotherapy in the recent treatment strategy for patients with metastatic or recurrent esophageal squamous cell carcinoma. *International Journal of Clinical Oncology* **23**(3), 466–472.

Hiramoto S, Hori T, Inoue A, *et al.* (2019) Prognostic factors in patients who received end-of-life chemotherapy for advanced cancer. *International Journal of Clinical Oncology* **24**(4), 454–459.

Hui D, Meghan S, Bruera E, *et al.* (2013) Targeted agent use in cancer patients at the end-of-life. *Journal of Pain and Symptom Management* **46**(1), 1–8.

Inoue SK, van Dyck CH, Alessi CA, *et al.* (1990) Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Annals of Internal Medicine* **113**(12), 941–948.

Inoue A, Kobayashi K, Usui K, *et al.* (2009) First line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. *Journal of Clinical Oncology* **27**(9), 1394–1400.

Kao S, Shafig J, Adams D, *et al.* (2009) Use of chemotherapy at end of life in oncology patients. *Annals of Oncology* **20**(9), 1555–1559.

Maltoni M, Scarpi E, Nanni O, *et al.* (2016) Systematic versus on-demand early palliative care: A randomized clinical trial assessing quality of care and treatment aggressiveness near the end-of-life. *European Journal of Cancer* **69**, 110–118.

Morita T, Bito S, Uchitomi Y, *et al.* (2005) Development of a clinical guideline for palliative sedation therapy using the Delphi method. *Journal of Palliative Medicine* **8**(4), 716–729.

Näppä U, Lindqvist O, Rasmussen BA, *et al.* (2011) Palliative chemotherapy during the last month of life. *Annals of Oncology* **22**(11), 2375–2380.

Petra G, Aynharan S, Theresas T, *et al.* (2015) Variations in intensity of end-of-life cancer therapy by cancer type at a Canadian tertiary cancer centre between 2003 and 2010. *Supportive Care in Cancer* **23**(10), 3059–3067.

Prigerson HG, Bao Y, Shah M, *et al.* (2015) Chemotherapy use, performance status, and quality of life at the end of life. *JAMA Oncology* **1**(6), 778–784.

Schinipper LE, Smith TJ, Raghavan D, *et al.* (2012) American society of clinical oncology identifies five key opportunities to improve care and reduce costs: The top five list for oncology. *Journal of Clinical Oncology* **30**(14), 1715–1724.

Tsai H-Y, Chung K-P and Kuo RN-C (2018) Impact of targeted therapy on the quality of end-of-life care for patients with non-small-cell lung cancer. *Journal of Pain and Symptom Management* **55**(3), 798–807.