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ORIGINAL ARTICLE

Prognostic factors in patients who received end-of-life chemotherapy for advanced cancer

Shuji Hiramoto[1] · Tomoko Tamaki[2] · Kengo Nagashima[3] · Tetsuo Hori[1] · Ayako Kikuchi[1] · Akira Yoshioka[1] · Akira Inoue[4]

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Abstract

Background Clinical efficacy of aggressive end-of-life (EOL) chemotherapy remains unclear.

Method Medical records of patients with advanced cancer between August 2011 and August 2016 were retrospectively analyzed. The primary endpoint was to identify prognostic factors at the last administration of chemotherapy. The secondary endpoint was to analyze the relationship between EOL symptoms and EOL treatment details.

Results Among 300 evaluated patients, the number of patients who died within 14 and 30 days from the last administration of chemotherapy were 16 (5.3%) and 50 (16.7%), respectively. Multivariate analysis revealed that ECOG-PS (OR 3.698, $p < 0.001$) and GPS2 (OR 3.791, $p = 0.028$) were significant prognostic factors. The MST of patients with both PS 2–4 and GPS2 (+) was 38 days, while that in patients with both PS 0–1 and GPS2 (−) was 134.5 days. The prevalence rate of nausea and vomiting (25.0%) and the mean hydration volume (0.50 L/day) in patients who died within 30 days from the chemotherapy was significantly higher than others (7.4%) (0.20 L/day).

Conclusion ECOG-PS and GPS were significant prognostic factors for aggressive EOL chemotherapy. Information on these factors may aid clinical decision-making in terms of risk–benefit balance, particularly in patients with poor prognosis.

Keywords End-of-life · Chemotherapy · Glasgow Prognostic Score · Prognostic factor

Introduction

Clinical efficacy of aggressive chemotherapy for end-of-life (EOL) patients with advanced cancer remains unclear, thus appropriate timing of chemotherapy cessation should be investigated. Earle reported that such aggressive chemotherapy has resulted in an increase in emergency department visits, hospitalization, and admissions to intensive care units in the last month of life in patients with advanced cancer [1]. African American patients were more likely to receive aggressive care, meanwhile the local availability of hospices was associated with less EOL chemotherapy. According to this report, EOL chemotherapy was tentatively defined as the last administration of chemotherapy to patients within 14 days or 30 days prior to death. In recent studies, rates of the last administration of chemotherapy within 14 days and 30 days to death were reported to be 3.0–11.6% and 6.3–18.8%, respectively [1–7]. Kao reported that younger age, cancer type, and chemo-sensitivity of the tumor were predictive factors for performing EOL chemotherapy in the last week before death [6] and Petra reported that breast, hematological, and gynecological cancer patients were 2.5 times more likely to undergo EOL chemotherapy than other cancer patients [7].

By knowing prognostic factors of EOL chemotherapy, oncologists can appropriately terminate the treatment and consider prompt discussions with patients about EOL care including a referral to hospice and palliative care services.

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✉ Shuji Hiramoto
otomari1rx.8@gmail.com

[1] Department of Clinical Oncology and Palliative Medicine, Mitsubishi Kyoto Hospital, Kyoto, Japan

[2] Department of Nursing, Mukogawa Woman's University, Nishinomiya, Japan

[3] The Institute of Statistical Mathematics, Tachikawa, Japan

[4] Department of Palliative Medicine, Tohoku University School of Medicine, Sendai, Japan

Therefore, we conducted this study to examine prognostic factors in patients who receive EOL chemotherapy and relationship between EOL symptoms and EOL chemotherapy.

Methods

Patients

We retrospectively analyzed patients who died of advanced cancer after receiving non-curative intent chemotherapy at our general acute hospital, Mitsubishi Kyoto Hospital, from August 2011 to August 2016. At our department, physicians can provide both oncology treatment such as chemotherapy and specialized palliative care including EOL care. From electronic medical records, patients aged 20 years or older who were diagnosed with locally advanced or metastatic cancer and treated with at least one admission of chemotherapy were included to this study. Patients with missing important data such as the date of the last administration of chemotherapy and those who received hormone therapy were excluded.

Procedure and endpoints

The primary endpoint of this study was to identify prognostic factors at the last administration of chemotherapy. The secondary endpoint was to analyze the relationship between EOL symptoms and EOL treatment details. We also divided the patients into two groups (patients who died within 30 days from the last administration of chemotherapy and those more than 30 days from the chemotherapy) and examined differences between the groups.

We collected baseline data before the chemotherapy regarding age, sex, clinical stage, Eastern Cooperative Oncology Group performance status (ECOG-PS), Glasgow Prognostic Score (GPS) consisting of the serum CRP and albumin levels [8], primary cancer site and its histology, details of comorbidity, the number of prior chemotherapy regimen, and details of the last chemotherapy. In the prognostic analysis, we used above factors in univariate and multivariate analysis.

Regarding EOL symptoms, our palliative care physician took care of each patient as daily clinical practice. Delirium was diagnosed using the Confusion Assessment Method [9]. 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 last 3 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 [10]. The amount of opioids administered was recorded in terms of the oral morphine-equivalent dose.

Statistical analysis

Time-to event-curves were calculated using the Kaplan–Meier method and compared using log-rank tests. Cox's proportional hazard models were used to evaluate prognostic factors. Statistical influence was presented and interpreted based on univariate and multiple logistic regression models (ORs) and 95% confidence intervals (CIs). A p value of <0.05 was considered statistically significant. All analyses were performed using JMP-Pro 13.0.0 (SAS Inc.).

Ethical considerations

The 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, Labor and Welfare in Japan. The hospital institutional review board approved this study.

Results

Patient background

Among 510 patients who died at our institute in this study period, 171 patients received supportive care only, thus 339 patients who underwent chemotherapy were eligible for this study. Among them, 39 patients were excluded due to loss of information about the last administration of chemotherapy. The numbers of patients who died within 14 and 30 days from the last administration of chemotherapy were 16 (5.3%) and 50 (16.7%), respectively, (Fig. 1). No patient died within 3 days from the last chemotherapy. The patients' background and details of the last chemotherapy are described in Table 1 and supplemental Table 1, respectively.

Prognostic analysis

In multivariate analysis of prognosis at the EOL chemotherapy, ECOG-PS (OR 3.698, $p<0.001$) and GPS2 (OR 3.791, $p=0.028$) were significant prognostic factors. The median survival time (MST) from the last administration of chemotherapy stratified with ECOG-PS and GPS2 levels was significantly different (Fig. 2). The MST of patients with both PS 2–4 and GPS2 (+) was 38 days, while that in patients with both PS 0–1 and GPS2 (−) was 134.5 days. Older age ($\geq$67 years old) (OR 2.074, $p=0.078$), recurrent stage (OR 0.405, $p=0.057$), and GPS1 (OR 3.306, $p=0.059$) showed a statistically significant trend (Table 2).

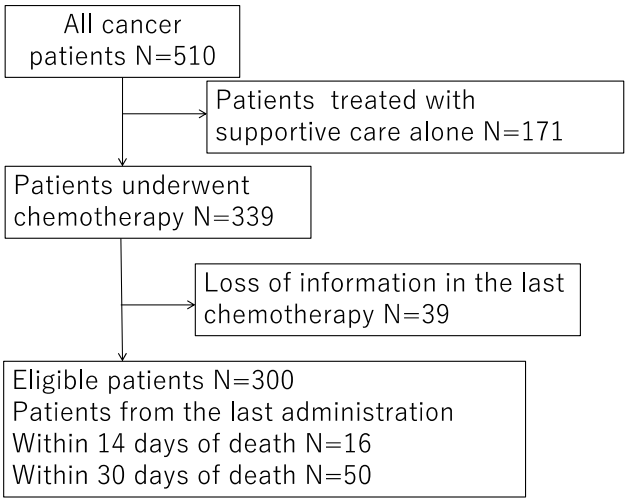

Fig. 1 Patient selection flow

Prevalence of EOL symptoms and details of EOL treatments

The prevalence rate of nausea and vomiting in patients who died within 30 days from the chemotherapy was 25.0%, which was significantly higher than that in patients who died more than 30 days from the chemotherapy (7.4%). The mean hydration volume (0.50 L/day) in patients who died within 30 days from the chemotherapy was significantly higher than that in patients who died more than 30 days from the chemotherapy (0.20 L/day) (Table 3).

Discussion

In this study, ECOG-PS and GPS were significant prognostic factors in patients with advanced cancer who received the last chemotherapy in their EOL stage. To the best of our knowledge, it is the first study that analyzed prognostic factors of EOL chemotherapy.

Palliative chemotherapy is used to improve the quality of life (QOL) of patients with advanced cancer; however, previous studies have reported that it would not improve the QOL of patients with poor PS [11]. Our study also suggests the ECOG-PS should be considered in the administration of chemotherapy. Similarly, GPS previously known as a prognostic factor in patients with advanced non-small-cell lung cancer, gastric cancer, colorectal cancer, pancreatic cancer, and esophageal cancer [8, 12–17] was revealed to be quite important to decide the eligibility of chemotherapy as well. Since GPS reflects the status of systemic inflammation in patients, it is reasonable that it influences a prognosis of patients who received aggressive chemotherapy. There was a significant difference between survival time in patients' group stratified by ECOG-PS and GPS2. This combination of prognostic factors can assist oncologists to decide the timing of chemotherapy cessation in terms of risk–benefit balance and to refer to proper palliative care specialists.

This analysis also suggests that EOL chemotherapy might worsen the QOL of patients although patient-reported-outcome was not examined. Patients who died within 30 days from the last chemotherapy suffered from nausea and vomiting more probably due to adverse effect of chemotherapy. High hydration volume observed in same group was also well known to deteriorate patients' QOL in EOL stage. From these points of view, prognosis at the administration of chemotherapy should be considered carefully.

This study has several limitations. First, since it was a retrospective study conducted in a single institution in Japan, current findings may be less reliable to be generalized, thus further validation is warranted. Second, the last chemotherapy included in a few immune-checkpoint inhibitor in this study because nivolumab was approved in the end of 2015 in Japan. The number of patients treated with molecular targeted monotherapy against cancers with driver mutations were also small although the reason remains unclear. Since the risk–benefit balance of these agents are much different from that of former cytotoxic agents and some of them are recommended for patients even with poor PS [18], the effect of EOL chemotherapy with them should be evaluated separately.

In conclusion, ECOG-PS and GPS were significant prognostic factors for aggressive EOL chemotherapy. Information on these factors may aid clinical decision-making in terms of risk–benefit balance, particularly in patients with poor prognosis. Further evaluation of EOL chemotherapy is warranted.

Table 1 Patients background

	All patients (%) $N=300$	Over 30 days of death (%) $N=250$	Within 30 days of death (%) $N=50$	p value
Age median	71.0	71.0	66.5	0.002
Sex				0.523
Male	186	153 (82.3)	33 (17.7)	
Female	114	97 (85.1)	17 (14.9)	
Clinical stage (UICC-7)				0.039
II–III	14	12 (85.7)	2 (14.3)	
IV	187	148 (79.1)	39 (20.9)	
Recurrence	99	90 (90.9)	9 (9.1)	
ECOG-PS				< 0.001
0.1	144	131 (91.0)	13 (9.0)	
2–4	118	81 (69.0)	37 (1.0)	
Unknown	38	38 (100)	0 (0)	
Comorbidity				0.193
Cardiac-Renal	32	31 (96.9)	1 (3.1)	
Respiratory	19	15 (78.9)	4 (21.1)	
Metabolic disease	50	42 (84.0)	8 (16.0)	
Mental/cranial nerve system	48	44 (91.7)	4 (8.3)	
Others	14	10 (71.4)	4 (28.6)	
Total number of comorbidity ≥ 2	34	31 (91.2)	3 (8.8)	
Median CRP level (average)	0.92 (2.74)	0.77 (2.18)	4.02 (5.17)	< 0.001
Median ALB level (average)	3.30 (3.18)	3.30 (3.24)	2.90 (2.92)	< 0.001
Glasgow Prognostic Score (GPS)				< 0.001
GPS 0	76	72 (94.7)	4 (5.3)	
GPS 1	68	55 (80.9)	13 (19.1)	
GPS 2	103	75 (72.8)	28 (27.2)	
GPS unknown	53	48 (90.6)	5 (9.4)	
Primary cancer site				0.827
Gastro-esophageal	82	65 (79.3)	17 (20.7)	
Biliary-pancreatic	60	49 (81.7)	11 (18.3)	
Colorectal	53	45 (84.9)	8 (15.1)	
Lung	41	34 (82.9)	7 (17.0)	
Breast	11	9 (81.8)	2 (18.2)	
Urological and gynecological	18	16 (88.9)	2 (11.1)	
Hepatocellular carcinoma	5	5 (100)	0 (0)	
Others	30	27 (90.0)	3 (10.0)	
Pathological findings				0.134
Adeno carcinoma	138	117 (84.8)	21 (15.2)	
Squamous cell carcinoma	41	34 (83.0)	7 (17.0)	
Undifferentiated	27	20 (74.1)	8 (25.9)	
Small cell carcinoma, Neuroendocrine carcinoma	20	17 (85.0)	2 (15.0)	
Others	34	32 (94.1)	2 (5.9)	
Unknown	40	30 (75.0)	10 (25.0)	
Chemo-line				0.169
1	118	94 (79.7)	24 (20.3)	
≥ 2	182	156 (86.7)	26 (13.3)	
Molecular targeted agents monotherapy	45	38 (84.4)	7 (15.6)	0.828
Cytotoxic agents = 1	178	149 (83.7)	29 (16.3)	0.833
Cytotoxic agents ≥ 2	77	63 (81.8)	14 (18.2)	0.679

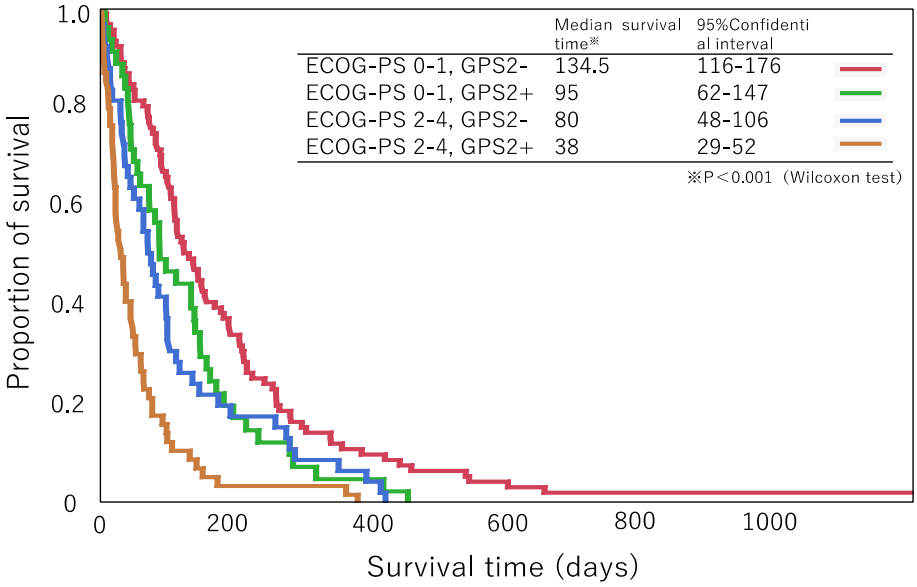

Fig. 2 Survival time from the last administration of chemotherapy for patients stratified by ECOG-PS and GPS2 (Kaplan Meier Survival curve)

Table 2 Prognostic factors analysis for the last administration of chemotherapy

Prognostic factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% Confidence interval	*p* value	Odds ratio	95% Confidence interval	*p* value
Age						
≧67/<67	1.942	1.049–3.597	0.035	2.074	0.922–4.673	0.078
Sex						
Male/female	1.231	0.650–2.329	0.524	1.229	0.553–2.733	0.613
Clinical stage						
Recurrence/stage II–IV	0.390	0.181–0.840	0.016	0.405	0.160–1.028	0.057
ECOG-PS						
2–4/0–1	4.603	2.362–9.479	<0.001	3.698	1.709–8.001	<0.001
Number of comorbidities						
≧2/0–1	0.451	0.132–1.537	0.203	0.452	0.091–2.250	0.332
GPS1						
GPS1/GPS0	1.086	0.517–2.181	0.822	3.306	0.957–11.428	0.059
GPS2						
GPS2/GPS0	2.789	1.445–5.523	0.002	3.791	1.154–12.459	0.028
Primary site						
EG, BP/others	1.507	0.818–2.778	0.189	1.160	0.541–2.487	0.703
Pathological findings						
POR, SCC, NEC/Others	1.439	0.662–3.127	0.358	1.022	0.337–3.098	0.969
Chemo-line						
≧2/1	0.652	0.351–1.216	0.177	0.519	0.227–1.184	0.119
Cytotoxic agents						
≧2/1, MTAs	1.136	0.575–2.243	0.714	0.882	0.381–2.095	0.776

EG esophageal-gastric cancer, *BP* biliary-pancreatic cancer, *POR* poorly differentiated, *SCC* small cell carcinoma, *NEC* neuroendocrine carcinoma

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

	Prevalence of end-of-life treatment					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)
Within 30 days	12.5%	18.8%	13.0%	25.0%	50.0%	0.50 ± 0.09	31%	20.6 ± 15.95
More than 30 days	29.9%	29.9%	22.0%	7.4%	22.0%	0.20 ± 0.02	27%	43.3 ± 3.79
p value	0.135	0.339	0.375	0.013	0.268	< 0.001	0.718	0.168

Compliance with ethical standards

Conflict of interest All the authors have approved the submission of this manuscript to your journal. There are no conflicts of interest to declare.

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