

Prognostic Factors and Clinical Characteristics in Elderly Patients with Advanced Cancer at the End-of-Life

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Abstract

Purpose: End-of-life characteristics, indicators of palliative care, and their prognosis in especially elderly cancer patients remain unclear.

Methods: We retrospectively analysed 510 patients who died of advanced cancer at our hospital from August 2011 to August 2016. We divide into categories elderly patients (80 years and older) (N=140) and non-elderly patients (under 80 years old) (N=370). The primary endpoint was to identify prognostic factors in elderly patients with advanced cancer at the end of life. The secondary endpoint was to analyse the relationship between details of end-of-life symptom, treatment, and their age.

Results: Background as follows: Male and female were 306 and 204. Patients with gastro-oesophageal, biliary-pancreatic, colorectal, lung, breast, urological and gynaecological, hepatocellular, and others were 114, 98, 82, 84, 25, 36, 20, and 51 by primary cancer site. ECOG-Performance Status was 12 in 0.1, and 498 in 2-4. In multivariate analysis of prognosis in elderly patients at the end-of-life, sex (HR1.252, p=0.041) and consciousness level (HR 1.714, p=0.048) were significant prognostic factors. The prevalence rate of cancer pain in elderly patients was 19.3%, which was significantly lower than in non-elderly (31.4%). Fatigue in elderly patients was 27.9%, which was significantly lower than in non-elderly (37.6%). Continuous deep sedation usage in elderly patients was 12.9%, which was significantly lower than in non-elderly (28.9%). The mean opioid dose in elderly patients was 23.3mg/day, which was significantly lower than that in non-elderly patients (43.8mg/day).

Conclusions: Consciousness level and sex were significant prognostic factors in elderly patients at the end of life. The prevalence rate of end-of-life symptoms was lower, the end-of-life intervention includes anti-cancer treatment in elderly patients was more reluctant than non-elderly.

Keywords: Elderly patients; End-of-life care; Prognostic factor

Introduction

It's known that total cancer deaths accounted for one-third and the leading cause of death in Japan. Moreover, Japanese people have one of the world's highest-life expectancy. While elderly cancer patients go on increase, their anti-cancer treatment and end-of-life care has become a problem to be solved. Discussion about clinical efficacy of anti-cancer treatment for end-of-life patient with advanced cancer was important to decide the timing of intensive treatment cessation in terms of risk-benefit balance and to refer to proper palliative care specialists [1-3]. There were some reports about end-of-life characteristics and palliative care provision for elderly cancer patients depend on primary cancer site [4, 5].

In palliative care settings, prognostic information is important for patients, their families, and their clinicians to decide on goals and priorities for end-of-life care. Palliative specialists used to implement typical prediction models to predict survival accurately [6-12]. But there are no models for the expanding oldest-old cancer patients.

The prevalence of several distressing symptoms, such as delirium, dyspnea, and anorexia, increases toward the end of life [13,14]. The prevalence and medical treatment of these distressing symptoms at the end-of-life stage may be different for their age.

If we can get information prognosis and clinical characteristics of elderly cancer patient at the end-of-life, this indicates that clinicians can deliver information to patients and their families and provide end-of-life care in advance for improvement of their experiences. There was no literature focused on elderly patients through the end-of-life from the anti-cancer treatment phase. Therefore, the aim of this study was to analyse in end-of-life prognosis and characteristics for elderly patients with advanced cancer.

Methods

Patients and Endpoints

We retrospectively analysed patients who died of advanced cancer at our palliative care unit (PCU) from August 2011 to August 2016. From electronic medical records, patients aged 20 years or older who were diagnosed with locally advanced or metastatic cancer were included to this study. It has been defined over 75 years old as "the late elderly" by the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society in Japan [15]. Definite of elderly patients is as over 70 or 75 years old for aggressive cancer treatment but were unknown in cancer palliative settings. If the cut-of value in elderly would define as 75 years and older, it is difficult to characterize the elderly due to number volume in this study. Therefore, we define elderly patients as 80 years and older. We divide into categories elderly patients (80 years and older) and non-elderly patients (under 80 years old) and analysed. Regarding of details of end-of-life anti-cancer treatment, we collected treatment lines and details in last administration of anti-cancer agent.

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The number of elderly patients was 140 (27.5%) and non-elderly 370 (72.5%). Among 510 patients who died at our institute in this study period, 171 patients received supportive care only. Among them, 31 patients were excluded to analyse about the last administration of anti-cancer treatment due to loss of information (Figure 1).

The primary endpoint was to identify prognostic factors in elderly patients with advanced cancer at the end-of-life in PCU. The secondary endpoint was to analyse the relationship between details of end-of-life care and anti-cancer treatment and their age.

Procedure

We collected baseline data regarding sex, primary cancer site, clinical stage, number of comorbidities, number of metastatic sites, Eastern Cooperative Oncology Group performance status (ECOG-PS), consciousness level, the serum calcium level, the serum albumin levels, the serum sodium (Na) level, the serum C-reactive protein (CRP) levels and prevalence of received chemotherapy. Consciousness level was classified into deep coma (300), coma (200), semi coma (100), stupor (30), hypersomnia (20), drowsiness (10), delirium (3), confusion (2), senselessness (1) and normal (0) in accordance with the Japan Coma Scale [16]. We defined 10-300 as poor consciousness and 0-3 as normal. In the prognostic analysis, we used above factors in univariate and multivariate analysis.

Regarding end-of-life symptoms, we collected prevalence of last three days of their life in cancer pain, delirium, nausea and vomiting, fatigue and dyspnea by our palliative care physician who took care of each patient as daily clinical practice. Delirium was diagnosed using the Confusion Assessment Method [17]. The prevalence of distressing symptoms and details of end-of-life 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 [18]. The amount of opioids administered was recorded in terms of the oral morphine-equivalent dose.

Statistical analysis

Time to event curves was 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 (HRs) 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

The patient's background as follows: Male and female were 306 and 204. Patients with gastro-oesophageal, biliary-pancreatic, colorectal, lung, breast, urological and gynaecological, hepatocellular and others were 114, 98, 82, 84, 25, 36, 20 and 51 by primary cancer site. ECOG-Performance Status was 12 in 0.1, and 498 in 2-4 (Table 1).

The rate of more than one in lines of anti-cancer treatment for elderly patients was 44.4%, which was lower than non-elderly patients (65.4%). The rate of more than one type of cytotoxic agent in last regimen for elderly patients was 13.3%, which was lower than non-elderly patients (30.8%) (Table 2).

Relationship between survival time and their age

Survival time from the diagnosis to death was 243.0 days in elderly and 406.5 days in non-elderly. From the last administration of anti-cancer agent to death were 89.0 days in elderly and 91.5 days in non-elderly. Time from the admission in PCU to death was 14.0 days in elderly and 12.0 days in non-elderly. There was no significant difference between elderly and non-elderly patient in each survival time (Table 3).

Prognostic analysis at the end-of-life by their age

In multivariate analysis of prognosis in elderly patients at the end-of-life, sex (HR 1.252, p=0.041) and consciousness level (HR 1.714, p=0.048) were significant prognostic factors (Table 4). In end-of-life expectancy from last admission in PCU stratified by sex and consciousness level, female elderly patients with normal consciousness level (JCS 0-3) (19 days) have significantly longer than male elderly with poor (2 days). In non-elderly patients at the end-of-life, consciousness level (HR 2.754, p<0.0010) and serum calcium level (HR 1.702, p<0.001) were significant prognostic factors (Table 5).

Prognostic analysis at the end-of-life by their age

The prevalence rate of cancer in elderly patients was 19.3%, which was significantly lower than in non-elderly patients (31.4%). The

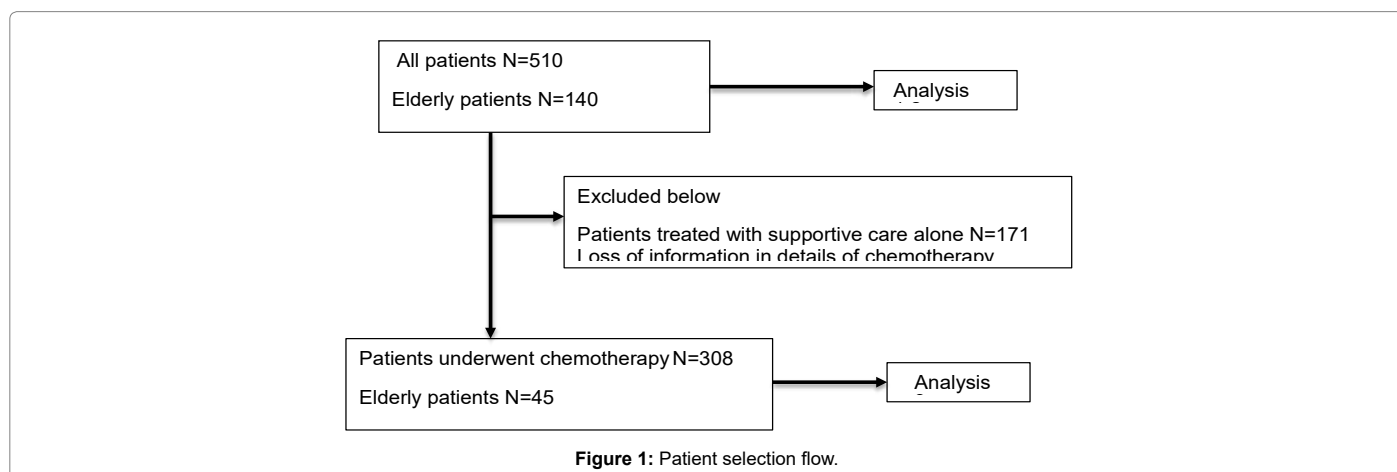


Figure 1: Patient selection flow.

	All Patients (%) N=510	Elderly (%) N=140	Non-elderly (%) N=370	P-value
Age Median (Average)	73.0(72.2)	84.0(84.6)	69.0(67.4)	<0.001
Sex				
Male	306	74(24.2)	232(75.8)	0.043
Female	204	66(32.4)	138(67.6)	
Clinical Stage (UICC-7)				
II-III	39	19(48.7)	20(51.3)	
IV	299	83(27.8)	216(72.2)	0.01
Recurrence	166	37(22.3)	129(77.7)	
Unknown	6	1	5	
ECOG-PS				
0.1	12	3(25.0)	9(75.0)	0.847
2-4	498	137(28.1)	361(71.9)	
Consciousness level				
0	285	66(23.2)	219(72.8)	0.05
1-3	143	47(32.9)	96(67.1)	
10-300	82	27(32.9)	55(67.1)	
Primary cancer site				
Gastro-esophageal	114	22(19.3)	92(80.7)	
Biliary-pancreatic	98	35(35.7)	63(64.3)	
Colorectal	82	17(20.7)	65(79.3)	
Lung	84	28(33.3)	56(66.7)	0.074
Breast	25	5(20.0)	20(80.0)	
Urological and Gynecological	36	11(30.6)	25(69.4)	
Hepatocellular Carcinoma	20	8(40.0)	12(60.0)	
Others	51	14(27.5)	37(72.5)	
Metastatic site				
Liver	161	38(23.6)	123(76.4)	
Lung	80	18(22.5)	62(77.5)	
Bone	79	14(17.7)	65(82.3)	0.008
Peritoneum	140	34(24.3)	106(75.7)	
CNS	52	12(23.1)	40(76.9)	
Others	141	31(22.0)	110(78.0)	
Total number of metastatic site ≥ 2	174	35(20.1)	139(79.9)	
Comorbidity				
Cardiac-Renal	72	27(37.5)	45(62.5)	
Respiratory	34	9(26.5)	25(73.5)	
Metabolic Disease	81	21(25.9)	60(74.1)	0.16
Mental/ Cranial Nerve system	90	39(43.3)	51(56.7)	
Others	24	8(33.3)	16(62.7)	
Total number of comorbidity ≥ 2	73	25(34.2)	48(65.8)	
Median serum CRP level (Average)	6.5(8.6)	6.5(19.8)	6.5(8.8)	0.708
Median serum ALB level (Average)	2.5(2.6)	2.5(2.1)	2.5(2.6)	0.94
Median serum Na level	136(136)	137(135)	136(136)	0.007
Median serum Ca level	10.2(10.2)	10.2(10.9)	10.1(10.2)	0.667
Presence of Chemotherapy (without loss of detail information)	322	47(32.1)	275(45.4)	<0.001

Table 1: Patients Background at the admission in PCU.

Prevalence of end-of-life symptom					
	Cancer Pain (%)	Delirium (%)	Nausea and Vomiting (%)	Fatigue (%)	Dyspnea (%)
Elderly (N=140)	# 19.3	31.4	2.9	27.9	21.4
Non-elderly (N=370)	# 31.4	29.5	6.8	37.6	22.4
P-value	0.007	0.665	0.09	0.04	0.781
Details in end-of-life treatment					
	Mean of hydration (L/day)	Continuous Deep Sedation (%)	Mean opioid dose (mg/day)	mOS from diagnosis(day)	mOS from admission to death(day)
Elderly (N=140)	0.25	12.9	23.3	464	22
Non-elderly (N=370)	0.225	28.9	43.8	750	21
P-value	0.873	<0.001	<0.001	0.155	0.684

Table 2: Relationship between end-of-life details and their age (N=510).

Reason for why discontinuation of anti-cancer treatment				
	Chemo line>1	Performance status in last administration>1	Number of cytotoxic agent in last administration>1	By image diagnosis (ID)
Elderly (N=45)	20 (44.4)	19 (42.2)	6 (13.3)	11
Non-elderly (N=263)	172 (65.4)	95 (36.1)	81 (30.8)	75
P-value	0.007	0.203	0.016	0.574
Reason for why discontinuation of anti-cancer treatment				
	By clinical diagnosis(CD)	By adverse event(AD)	By patients' demand(PD)	By completion
Elderly (N=45)	12	9	4	0
Non-elderly (N=263)	77	36	8	9
P-value	0.721	0.268	0.061	0.208
Reason for why discontinuation of anti-cancer treatment				
	By acute death	By decline of performance status(PS)	By others	Unknown
Elderly (N=45)	2	7	4	2
Non-elderly (N=263)	14	38	0	0
P-value	0.806	0.846	0.405	0.557

Table 3: Relationship between details of anti-cancer treatment and their age (N=308).

Prognostic factor		Univariate analysis			Multivariate analysis		
		HR	95%Confidential interval	P-value	HR	95%Confidential interval	P-value
Sex	Male/Female	1.252	0.892-1.759	0.194	1.531	1.017-2.323	0.041
Primary site	EG,BP/Others	0.953	0.675-1.334	0.779	1.105	0.702-1.742	0.667
Clinical Stage	Recurrence/Stage II-IV	1.12	0.758-1.620	0.561	1.017	0.638-1.595	0.941
Number of comorbidity	≥2/0-1	1.138	0.719-1.731	0.567	1.403	0.819-2.318	0.211
Number of meta	≥2/0-1	1.291	0.864-1.881	0.206	1.159	0.695-1.879	0.563
ECOG-PS	2-4/0-1	1.364	0.515-5.540	0.577	1.58	0.564-6.599	0.421
Consciousness level	10-300/0-3	1.12	0.758-1.620	0.561	1.714	1.006-2.827	0.048
Ca	>10.3/≤10.3	1.1	0.756-1.589	0.615	0.979	0.629-1.533	0.925
ALB	<3.5/≥3.5	1.601	0.886-3.209	0.125	1.172	0.566-2.645	0.681
Na	<135/≥135	1.317	0.919-1.869	0.132	1.348	0.851-2.092	0.199
CRP	>1.0/≤1.0	1.848	1.137-3.181	0.012	1.595	0.908-2.971	0.107
Chemotherapy	+/-	0.885	0.615-1.258	0.501	0.911	0.594-1.374	0.66

Table 4: Prognostic factors analysis for survival time of the elderly patients (over 80 years old) in end-of-life settings (N=140).

Abbreviation: EG: Esophageal-Gastric Cancer; BP: Biliary-Pancreatic Cancer; HR: Hazard Ratio

Prognostic Factor		Univariate Analysis			Multivariate Analysis		
		HR	95% Confidential interval	P-value	HR	95% Confidential interval	P-Value
Sex	Male/Female	1.236	1.001-1.531	0.049	1.191	0.922-1.548	0.183
Primary site	EG,BP/Others	1.042	0.846-1.281	0.696	1.112	0.859-1.438	0.417
Clinical Stage	Recurrence/Stage II-IV	0.921	0.741-1.141	0.456	1.059	0.805-1.383	0.678
Number of comorbidity	≥2/0-1	1.076	0.784-1.444	0.643	1.097	0.742-1.582	0.635
Number of meta	≥2/0-1	0.835	0.675-1.030	0.092	0.822	0.527-1.070	0.146
ECOG-PS	2-4/0-1	2.862	1.439-6.799	0.002	1.46	0.592-4.853	0.445
Consciousness level	10-300/0-3	2.984	2.201-3.971	<0.001	2.754	1.909-3.880	<0.001
Ca	>10.3/≤10.3	1.549	1.211-1.975	<0.001	1.702	1.306-2.215	<0.001
ALB	<3.5/≥3.5	1.19	0.843-1.737	0.334	1.027	0.647-1.689	0.914
Na	<135/≥135	1.129	0.918-1.386	0.249	0.991	0.754-1.296	0.948
CRP	>1.0/≤1.0	1.443	1.055-2.026	0.021	1.473	0.979-2.277	0.064
Chemotherapy	+/-	1.024	0.804-1.319	1.024	1.144	0.852-1.554	0.376

Table 5: Prognostic factors analysis for survival time of the non-elderly patients (under 80 years old) in end-of-life settings (N=370).

Abbreviation: EG: Esophageal-Gastric Cancer; BP: Biliary-Pancreatic Cancer; HR: Hazard Ratio

prevalence rate of fatigue in elderly patients was 27.9%, which was significantly lower than non-elderly patients (37.6%). The prevalence rate of continuous deep sedation usage in elderly patients was 12.9%, which was significantly lower than non-elderly patients (28.9%). The mean opioid dose in elderly patients was 23.3mg/day, which was significantly lower than that in non-elderly patients (43.8mg/day) (Table 6).

Discussion

Survival time from the diagnosis, the last administration of anti-cancer agent and the last admission in PCU to death was less likely depending on their age. We reported that ECOG-PS and Glasgow Prognostic Scale [19,20] consist of serum C-reactive protein and serum albumin level were prognostic factor in end-of-life anti-cancer treatment, and there was no association between end-of-life anti-cancer treatment and their age [3]. Moreover, there was no association between prognosis and their age in prognostic prediction models at the end-of-life settings [6-11]. The intensity and number of lines in anti-cancer treatment for elderly patients was lower than non-elderly because we intend to choose less toxic regimen like mono therapy rather than toxic regimen for elderly patients in accordance of our domestic guideline [21].

Sex and consciousness level and were significant prognostic factors in elderly patients at the end-of-life, which serum calcium and consciousness level was significant in non-elderly patients. It was reported that sex was important factors in several research about cancer treatment but not in end-of-life prediction models. Sex might be a specific factor in elderly, which non-specific in non-elderly. Consciousness level in vice versa was common prognostic regardless age in end-of-life. In rerated to the consciousness level, delirium was known as prognostic factors in several end-of-life prediction models [7-9]. We must pay attention to especially male elderly patients with poor consciousness level because they left only two days in the median from admission to PCU.

In this study the prevalence rate of cancer pain and fatigue in elderly patients at the end-of-life was less than non-elderly. This result was very impact for us because there was no evidence focused on end-of-life symptom of elderly patients with advanced cancer. However, we must pay attention low consciousness level and cognitive functions were seen in elderly patient's background in this study. So, it could be difficult to reply on question about fatigue and pain especially in elderly patients for these reasons. The prevalence rate of continuous deep sedation and the amount of opioids usage was less than non-elderly. Though symptom of delirium was most often reason we must provide continuous deep sedation for end-of-life patients, there wasn't seen no significant difference by age. We thought the reason in the high rate of sedative intervention for non-elderly patients because of more complain about pain and fatigue than elderly patients.

To our best knowledge, this is first literature focused on elderly patients with advance cancer through the end-of-life from the anti-cancer treatment phase. However, 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, it's known some frail criteria to measure frailty are used to be in elderly patients. However, we couldn't measure relationship between frailty and end-of-life intervention because of retrospective study. Third, defined as elderly patients in end-of-life settings was ambiguous.

Conclusion

Consciousness level and sex were significant prognostic factors in elderly patients at the end-of-life. The prevalence rate of end-of-life symptom was lower, the end-of-life intervention include anti-cancer treatment in elderly patients was more reluctant than non-elderly.

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