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Palliative Chemotherapy for Patients with Pulmonary Pleomorphic Carcinoma: A Retrospective Single-institutional Study

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Abstract

Objective: Pulmonary pleomorphic carcinoma (PPC) is considered to be highly resistant to conventional standard chemotherapy for non-small cell lung cancer and associated with poor prognosis. Because of its histological rarity, the efficacy of palliative chemotherapy is not well-known. This study aimed to clarify the efficacy of palliative chemotherapy for this rare type of aggressive tumor.

Method: We retrospectively reviewed our medical records. We collected data on patients who had been histologically diagnosed of PPC and received palliative chemotherapy between June 2007 and December 2014 at Osaka Police Hospital.

Results: Among a total of 1461 primary lung cancers, 29 patients (2.0%) were diagnosed with PPC. Seventeen patients, including 15 males and 3 females, received palliative chemotherapy. Patients had the median age of 67 years (range, 43-80 years) and included twelve stage IV, four stage IIIB and one post-surgical recurrent diseases. Twelve patients received platinum-based regimen, while five were treated with monotherapy. The most frequent regimen in the first-line chemotherapy was combination of carboplatin plus paclitaxel. Response was found in a patient who had been treated with a triple combination of carboplatin, paclitaxel plus bevacizumab. The response rate (RR), disease control rate (DCR), median progression-free survival (PFS), median overall survival (OS) and 1-year survival rate of the first-line chemotherapy were 5.9% (95% confidence interval; 0.1-28.7%), 35.3% (14.2-61.7%), 45 days (35-115 days), 179 days (64-303 days) and 19.0% (4.7-40.6%), respectively. Among 15 regimens per 9 patients in the second- and further-line settings, none experienced response. The RR, DCR, median PFS, median OS and 1-year survival rate of the second-line chemotherapy (n=9) were 0% (0-28.3%), 33.3% (7.5-70.1%), 77 days (3-142 days), 144 days (5-331 days) and 11.1% (0.6-38.8%), respectively.

Conclusion: Palliative chemotherapy was futile for advanced PPC. Further investigation of a new approach to this aggressive tumor is required.

Keywords: Palliative chemotherapy; Pulmonary pleomorphic carcinoma; Non-small cell lung cáncer; Carboplatin plus paclitaxel; Bevacizumab; Second-line chemotherapy; Poor prognosis

Introduction

Pulmonary pleomorphic carcinoma (PPC) is defined as a coexistence tumor of a carcinomatous tumor with a sarcomatoid tumor component of at least 10%, according to the World Health Organization (WHO) histological classification of lung tumors 2004 [1]. This subtype of sarcomatoid carcinoma has been considered to be characteristic of worse prognosis than other histological types. Some recent retrospective studies have suggested that PPC is usually resistant to standard chemotherapeutic regimens for non-small cell lung cancer (NSCLC) [2-6]. Because of a low incidence of less than 0.4% of all pulmonary malignancies [7], there were limited reports on the efficacy of palliative chemotherapy and was no established treatment for advanced PPC. In this study, we retrospectively investigated 31 palliative chemotherapy regimens for 16 patients with advanced PPC. This study aimed to clarify the efficacy of palliative chemotherapy for this rare type of aggressive tumor.

Methods

Patient selection and study design

We collected data on patients who had been diagnosed of PPC between June 2007 and December 2014 at our hospital. PPC was diagnosed according to the WHO classification report 2004 [1]. A diagnosis was based on the light microscopic findings of histological specimens and, if necessary, confirmed by immunohistochemical examinations. The pathological diagnosis was made as a routine work by agreement of two independent pathologists. For this study, we did not review the past diagnosis. Our institutional ethics committee approved this study and waived the requirement for informed consent from each patient.

Assessment

Clinical staging and response to chemotherapy was assessed according to the seventh edition of TNM classification for malignant tumors by the International Union Against Cancer and the American Joint Committee on Cancer [8] and to the Response Evaluation Criteria for Solid Tumors, version 1.1 [9], respectively. Response

classification required two radiological assessments of over 6 weeks interval after the start of chemotherapy, unless confirmation of objective progressive disease (PD). We defined progression-free survival (PFS) and overall survival (OS) as the interval from the first day of chemotherapy to PD or death from any cause, and to the last day on which the patient was confirmed to be alive or dead from any cause, respectively. The Kaplan–Meier method estimated survival. We closed the data collection by December 31, 2015. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [10].

Results

Among a total of 1461 primary lung cancers at our institution between June 2007 and December 2014, 29 patients (2.0%) were histologically diagnosed with PPC. Among 17 and 7 patients whose epidermal growth factor receptor (EGFR) mutation status and anaplastic lymphoma kinase (ALK) gene rearrangement were examined, respectively, none harbored positive activated mutation status. Except for 3 non-smokers and 2 unknown smoking habit, 24 patients were current or ex-smokers. Among 19 patients with stage IIIB or IV at diagnosis, three did not receive chemotherapy. Among 10 patients with stage IB-IIIA, nine received surgery, and one patient with stage IIIA transferred to another hospital for aggressive treatment immediately after confirmed diagnosis. Among 5 patients who experienced post-surgical recurrence, two transferred to other hospitals for aggressive treatment, two received best supportive care alone, and one received palliative chemotherapy. Clinical characteristics of the 17 patients who received palliative chemotherapy at our institution are listed in Table 1.

Table 2 presents the details in the first-line chemotherapy. Twelve patients received platinum-based regimen, while the remaining 5 patients were treated with monotherapy. The response rate (RR), disease control rate (DCR), median PFS, median OS and 1-year survival rate of the first-line chemotherapy were 5.9% (95% confidence interval; 0.1-28.7%), 35.3% (14.2-61.7%), 45 days (35-115 days), 179 days (64-303 days) and 19.0% (4.7-40.6%) among 17 patients, and 8.3% (0.2-38.5%), 25.0% (5.5-57.2%), 44 days (35-161 days), 179 days (48-374 days) and 27.8% (6.7-54.5%) among 12 patients who received platinum-based regimens, respectively. Partial response (PR) was observed in a patient treated with a triplet of carboplatin, paclitaxel and bevacizumab.

No.	Sex	Age	Smoking	Pack-Years	Pathological characteristics		Diagnostic methods	c-stage
					Carcinomatous	Sarcomatous		
1	M	71	CS	50	Sq	Giant	Skin met	III B
2	M	72	Ex	112.5	Ad	Giant	TBB	III B
3	M	56	CS	27	Sq	Giant	Autopsy	III B
4	M	71	CS	75	Unidentified	Combined	TBB	IV
5	F	65	CS	45	Ad	Unidentified	TBB	IV
6	M	70	Unknown	Unknown	Ad	Spindle	Surgery	IV
7	F	50	CS	22.5	Ad	Unidentified	Brain met	IV
8	M	60	CS	61.5	Ad	Combined	TBB	IV
9	M	43	CS	30	Unidentified	Giant	TBB	IV
10	M	68	Ex	84	Ad	Spindle	TBB	IV
11	M	62	Ex	140	Ad	Giant	LN met	IV
12	M	67	Ex	40	Ad	Combined	TBB	IV
13	F	64	CS	43	Large	Giant	TBB	IV
14	M	78	Ex	40	Ad	Giant	Surgery	Recurrence
15	M	80	Ex	26.3	Ad	Giant	TBB	III B
16	M	61	CS	21	Unidentified	Giant	CTGB	IV
17	M	74	CS	37.5	Sq	Spindle	TBB	IV

Ad: Adenocarcinoma; CS: Current Smoker; CTGB: CT-Guided Needle Biopsy; Ex: Ex-smoker; F: Female; Giant: Giant Cell Carcinoma; Large: Large Cell Carcinoma; LN: Lymph Node; M: Male; met: Metastasis; Spindle: Spindle Cell Carcinoma; Sq: Squamous Cell Carcinoma; TBB: Trans-bronchial Biopsy

Table 1: Patient Characteristics.

No.	Regimens	PS	Courses	Response	PFS (days)	OS (days)
1	wCBDCA+wPTX+TRT→CBDCA+PTX	1	4	SD	187	303
2	CBDCA+PTX+Bev→Bev	1	10	PR	181	346
3	CBDCA+PTX	1	2	PD	42	69
4	CBDCA+wPTX	1	3	PD	89	156
5	CBDCA+wPTX	2	2	PD	35	72
6	CBDCA+wPTX	1	3	PD	86	437
7	CBDCA+wPTX	1	2	PD	45	475
8	CBDCA+wPTX	1	5	SD	161	374
9	CBDCA+wPTX	1	2	PD	39	179
10	CDDP+PEM	1	1	PD	25	30
11	CDDP+PEM	1	2	NE	43	50[1]
12	CBDCA+S-1	2	2	PD	35	48
13	Gefitinib	2	2[2]	PD	41	147
14	S-1	1	1	SD	64	64
15	S-1	1	3	SD	115	289
16	S-1	1	2	SD	176	214
17	S-1	3	1	PD	20	36

[1]Censored due to transfer to another hospital; [2]Twenty-one day administration of gefitinib was counted as one course; Bev: Bevacizumab; CBDCA: Carboplatin; CDDP: Cisplatin; OS: Overall survival; PD: Progressive Disease; PEM: Pemetrexed; PFS: Progression-free Survival; PR: Partial Response; PS: Performance Status; PTX: Paclitaxel; SD: Stable Disease; TRT: Thoracic Radiotherapy; w: Weekly

Table 2: First-line chemotherapy.

Table 3 shows the details in the second- and further-line chemotherapy. Among 15 regimens per 9 patients in the second- and further-line settings, four regimens were combination doublets of two non-platinum drugs, but the remaining 11 regimens were monotherapy. No regimen was responsive. The RR, DCR, median PFS, median OS and 1-year survival rate of the second-line chemotherapy (N=9) were 0% (0-28.3%), 33.3% (7.5-70.1%), 77 days (3-142 days), 144 days (5-331 days) and 11.1% (0.6-38.8%), respectively.

Discussion

This retrospective study reported on the efficacy of palliative chemotherapy for patients with advanced PPC, a rare histological subtype of lung tumor. As the previous reports suggested (Table 4), our study also showed that PPC was aggressively resistant to any regimens and resulted in poor prognosis. Thus, our study failed to propose any promising regimens for PPC.

No.	Line	Regimens	PS	Courses	Response	PFS (days)	OS (days)
1	2nd	DTX	2	1	PD	22	80
2	2nd	PEM	0	6	SD	132	144
3	2nd	S-1	1	4	PD	211	331
4	3rd	ERL	2	1[1]	PD	28	113
5	4th	GEM+VNB	2	1	PD	16	66
6	2nd	PEM+ERL	1	4	SD	77	385
7	3rd	DTX	1	6	PD	35	285
8	4th	GEM+VNB	2	2	PD	35	136

9	5th	wCPT-11	2	1	PD	21	66
10	2nd	DTX+TRT	2	6	SD	128	192
11	3rd	PEM	2	2	PD	41	63
12	2nd	GEM+VNB	2	3	PD	63	131
13	2nd	DTX	2	1	PD	3	5
14	2nd	S-1	3	1	PD	43	93
15	2nd	ERL	2	3[a]	PD	142	152

[1]Twenty-one day administration of erlotinib was counted as one course; CPT-11: Irinotecan; DTX: Docetaxel; ERL: Erlotinib; GEM: Gemcitabine; OS: Overall Survival; PD: Progressive Disease; PEM: Pemetrexed; PFS: Progression-free Survival; SD: Stable Disease; TRT: Thoracic Radiotherapy; VNB: Vinorelbine; w: Weekly

Table 3: Second- and further-line chemotherapy.

Author	Country	N[1]	Stage	Regimen (N[2])	RR DCR	PFS	OS	Survival rate
Bae [2]	South Korea	13	8 recurrence 5 advanced	CDDP+GEM (6) GEM+VNB (2) CDDP+PTX (2) CDDP+IFS+ETP (1) CDDP+VNB (1) Gef (1)	0% 15%	ND	5 m	1-Y 15%
Hong [3]	South Korea	12	9 recurrence 3 metastatic	CDDP+GEM (5) CBDCA+GEM (3) CBDCA+PTX (2) CDDP+DTX (1) CDDP+PTX (1)	17% 42%	3 m	8 m	1-Y 25% 2-Y 12.5%
Ito [4]	Japan	5	2 recurrence 3 advanced	CBDCA+PTX (3) CDDP+DTX (1) CBDCA+DTX (1)	0% 100%	ND	ND	ND
Kaira [5]	Japan	6	1 Recurrence 5 Advanced	CDDP+GEM (2) CBDCA+PTX (2) DTX (2)	0% 67%	1.8 m	8.5 m	1-Y 20%
Tamura [6]	Japan	13	9 recurrence 4 stage IV	CBDCA+PTX (6) CBDCA+GEM (2) DTX (2) Gef (2) CBDCA+ETP (1)	0% ND	1.5 m	7.5 m	ND
Our study	Japan	16	1 recurrence 4 stage IIIB 11 stage IV	CBDCA+PTX based (9) S-1 (4) CDDP+PEM (1) CBDCA+S-1 (1) Gef (1)	6% 38%	54.5 d	167.5d	1-Y 19%

[1]The number of patients who received chemotherapy; [2]The number of patients who received each régimen; CBDCA: Carboplatin; CDDP: Cisplatin; DCR: Disease Control Rate; DTX: Docetaxel; ETP: Etoposide; Gef: Gefitinib; GEM: Gemcitabine; IFS: Ifosphamide; m: Month; ND: Not Described; OS: Overall Survival; PEM: Pemetrexed; PFS: Progression-free Survival; RR: Response Rate; VNB: Vinorelbine; Y: Year.

Table 4: Review of previous case series reports of the first-line palliative chemotherapy for patients with pulmonary pleomorphic carcinoma.

Regarding carboplatin plus paclitaxel in our study, this combination doublet provided little response and was unsatisfactory for PPC. Except for a case report in which carboplatin plus paclitaxel successfully achieved tumor size reduction and long-term survival in two patients [11], no case series detected a responsive case treated with this doublet regimen [2-6]. We experienced an exceptional case in which bevacizumab-containing regimen achieved PR and provided favorable PFS, approximately six months. Three case reports described carboplatin, paclitaxel plus bevacizumab regimen achieved PR in four patients [12-14]. In addition, another case report described a case in which weekly paclitaxel plus bevacizumab was highly effective in the brain metastases after the completion of whole brain radiotherapy, but moderately effective in the thoracic lesions [15]. Although bevacizumab should be used for the highly aggressive tumor with careful attention to characteristic adverse effects of hemorrhage, this antibody drug may deserve further evaluation for PPC.

Cytotoxic chemotherapy containing platinum and gemcitabine is also debatable. Several case reports have described cases of PPC that responded to platinum plus gemcitabine. Hong et al. experienced two PR and two SD among eight patients treated with platinum plus gemcitabine as the first-line regimen [3]. Kaira et al. also found a case which achieved PR in the second-line carboplatin plus gemcitabine regimen [5]. Tamiya [16] and Yamanashi [17] et al. also reported successful cases in which cisplatin plus gemcitabine and carboplatin plus gemcitabine provided long-term response and survival, respectively. In contrast, the studies by Bae and Tamura et al. found no responder among 6 and 2 patients treated with platinum plus gemcitabine [2,6]. In our institution, gemcitabine was not used in the first-line regimen, and was not effective in combination with vinorelbine in the later-line setting.

This study has several limitations. First, this study was retrospective and our population was small sample size. Considering the rarity of this histology, a prospective and large scale study would be impossible. Our study was one of the largest studies which evaluated the palliative chemotherapy for advanced PPC. Second, our study included 11 cases in which pathological diagnosis was based on tiny specimens obtained by trans-bronchial biopsy or CT-guided biopsy. Except for post-surgical recurrence, it is usually difficult to obtain a sufficient amount of specimens from patients with already advanced stage of lung cancer at the diagnosis.

Conclusion

Palliative chemotherapy was futile for advanced PPC. Further investigation of a new approach to this unfavorable tumor is required.

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