進行・再発非小細胞肺癌初回治療終了後患者の観察研究（SAPPHIRE研究），初回報告

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Abstract

◆目的

通常診療において進行・再発非小細胞肺癌（NSCLC）の初回化学療法終了後患者の二次化学療法の実施率を検討

◆対象

進行・もしくは術後再発NSCLCの診断で，施設において連続した症例であり，初回化学療法としてプラチナ製剤＋第三世代抗癌剤の併用が開始された症例

◆方法

2010/4 以降の症例を観察研究として登録した。主として初回化学療法の種類，臨床効果（Non-PD，PD），維持化学療法の有無，及び二次化学療法実施の有無と不可能であった症例の理由について調査検討した。またこの研究はパブリックヘルスリサーチセンターがん臨床研究支援により実施

◆結果

登録症例は 2010/10 から 2011/9 までに全国 30 施設より 866 例の登録があった。全体の背景因子として性別（男/女；628/238），年齢分布（24－80，中間値 65），組織型（腺癌/扁平上皮癌/その他；603/174/89）。治療6ヶ月経過症例 592 例（2012年3月末）についての初回中間集計では，初回化学療法の効果 SD 以上の比率は 68.9%，維持化学療法の実施の有/無の比率（初回化学療法 PD 症例は除く）29/71%，二次化学療法実施（6ヶ月経過時点）の有/無の症例数は 264/135，その中で増悪が認められない 42 例以外で二次化学療法非実施例の主な理由は PS 低下 55，患者拒否 20，死亡 5 であった。

Background

- Second-line chemotherapy comprises the standard of care for non-small-cell lung cancer (NSCLC)[1-3].
- However, not all patients could receive appropriate 2nd-line chemotherapy.
- Recent studies demonstrated that maintenance chemotherapy prolongs survival in patients with NSCLC[4-7].
- Subgroup of patients who are benefited by maintenance chemotherapy is still to be determined.
- The proportion of patients who could not receive 2nd-line chemotherapy and the reason for undertreatment is not fully investigated.

Objectives

- To investigate the proportion of patients with NSCLC who received 2nd-line chemotherapy after platinum-based 1st-line chemotherapy.
- To elucidate the reasons and factors which hinder patients from receiving 2nd-line chemotherapy.

Methods

Study Design

- Cohort study

Primary Endpoint

- Proportion of patients who received 2nd-line chemotherapy after platinum-based 1st-line chemotherapy

Patient Inclusion

- Patients with advanced or recurrent NSCLC
- Platinum-based 1st-line chemotherapy between April 2010 and September 2011 from 30 institutions in Japan
- Platinum-naïve
- Without history of other malignancy

Data Collection

- Patient characteristics including age, gender, performance status (ECOG), smoking status, comorbidities (diabetes mellitus, cardiac disease, interstitial lung disease), body mass index, histological subtype, EGFR mutation, ALK translocation, CBC/chemistry at registration
- Details of 1st-, 2nd-, 3rd-line, and maintenance chemotherapy; including regimen, response
- Reason for administration or omitting 2nd-line chemotherapy
- Survival

Result

- Data cutoff at April 2012; updated from abstract submission
- Data of 866 patients were assessable for patient characteristics and details of 1st line treatment; 788 for response; 620 for maintenance chemotherapy; 547 for 2nd line chemotherapy; 479 for analysis of factors which hinders patients from receiving 2nd- line chemotherapy

Patient characteristics	Number of patients (N=866)	%
Age (median, years) (range)	65 (24 – 86)	
Gender male/female	628/238	72.5/27.5
PS (ECOG) 0/1/2/3-4	343/450/65/7	39.6/52.0/7.5/0.8
Comorbidities none/any	654/212	75.5/24.5
Histology		
adenocarcinoma	603	69.6
squamous cell carcinoma	174	20.1
large cell carcinoma	9	1.0
other	80	9.2
EGFR mutation (+)	88	10.2
exon21 L858R/exon19 del	42/36	4.8/4.2
EGFR mutation (−)	514	59.4
ALK translocation (+)/(−)/unknown	11/42/813	1.3/4.8/93.9
Smoking history		
never/experienced/current	174/435/252	20.1/50.2/29.1
Body mass index (median) (range)	22.1 (13-39.6)	

1st line Treatment delivery	Number of patients (N=866)	%
CDDP-based	332	38.3
CDDP+PEM/CDDP+PEM+BV	152/10	17.6/1.2
CDDP+GEM	51	5.9
CDDP+VNR	21	2.4
CDDP+DOC/CDDP+DOC+BV	47/20	5.4/2.3
CDDP+S-1	5	0.6
CBDCA-based	501	57.9
CBDCA+PEM/CBDCA+PEM+BV	125/28	14.4/3.2
CBDCA+GEM	30	3.5
CBDCA+PTX/CBDCA+PTX+BV	173/89	20.0/10.3
CBDCA+S-1	34	3.9
BV containing regimen	168	19.4

	Number of patients	%
Response to 1st line chemotherapy	788	100
CR/PR/SD/PD/NE	4/266/295/161/62	0.5/33.8/37.4/20.4/7.9
Maintenance therapy	620	100
none	429	69.2
PEM/PEM+BV	62/21	10.0/3.4
BV	67	10.8
Erlotinib	3	0.5
S-1/S-1+BV	13/11	2.1/1.8
Other	12	1.9
2nd-line chemotherapy	547	100
none	179	32.7
DOC	149	27.2
PEM	69	12.6
Erlotinib/Gefitinib	27/16	4.9/2.9
S-1	18	3.3
other	89	16.3

Result (cont.)

- 179 patients did not receive 2nd-line chemotherapy at the time of data cutoff; the reasons were as follows: without disease progression, 50 (27.9%); declined PS, 75 (41.9%); patient refusal, 28 (15.6%); death of any cause, 6 (3.4%).

Factor		2nd line therapy (N=479) Number of patients (%) No (n=125)	Yes (n=354)	Univariate P value*
male		98 (78.4)	254 (71.8)	p = 0.1587
female		27 (21.6)	100 (28.2)	
age	<65	43 (34.4)	168 (47.5)	**0.0120**
	≧65	82 (65.6)	186 (52.5)	
PS	0	31 (24.8)	170 (48.0)	**<0.0001**
	1-4	94 (75.2)	184 (52.0)	
Smoking	never	15 (12.0)	76 (21.5)	**0.0237**
	exp/current	110 (88.0)	278 (78.5)	
Comorbidity※	none	84 (67.2)	271 (76.6)	**0.0440**
	any	41 (32.8)	83 (23.4)	
BMI	<20	46 (36.8)	87 (24.6)	**0.0106**
	≧20	79 (63.2)	267 (75.4)	
EGFR	mutation (+)	5 (3.9)	30 (8.2)	0.2598
	mutation (−)	79 (61.2)	219 (59.5)	

*Fisher's test, ※DM, cardiac disease, ILD

Factor	Odds ratio	95% CI	Multivariate P value**
Age (≧65 vs <65)	0.648	0.416 – 1.011	0.0558
PS (1-4 vs 0)	0.395	0.247 – 0.631	**0.0001**
Smoking (ex/current vs never)	0.500	0.270 – 0.923	**0.0268**
Comorbidities (any vs no)	0.649	0.405 – 1.040	0.0722
BMI (≧20 vs <20)	1.565	0.989 – 2.477	0.0558

**Logistic regression model

Summary and Conclusion

- This is the largest cohort study exploring the proportion of patients with NSCLC and reasons for omitting 2nd-line chemotherapies.
- Maintenance therapy (either switch or continuation) was administered in approximately 30% of patients.
- Although data were immature, approximately 30% of patients did not receive appropriate 2nd-line chemotherapy.
- Declined PS was the most common reason for hindering 2nd-line chemotherapy.
- Advanced age, declined PS, smoking history, comorbidity, low BMI were correlated with hindrance to 2nd-line therapy in univariate analysis; however EGFR mutation was not significantly correlated.
- In multivariate analysis, declined PS and smoking history were associated with hindrance to 2nd-line chemotherapy.
- Further investigation to establish predictive model is currently underway.

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