Prospective study on incidence of bone metastasis (BM) and skeletal related events (SREs) in patients (pts) with stage IIIB and IV lung cancer (CSP-HOR13)

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BACKGROUND

- Although the overall incidence of BM is not known, bone metastases are a frequent complication in pts. with advanced lung cancer.
- Bone metastases can be associated with SRE, which include pathologic fracture, need for surgery or radiation to bone, spinal cord compression, and hypercalcemia of malignancy.
- As pts' quality of life deteriorates tremendously once SREs develop, it is important for investigators to treat pts. with bone metastasis with an appropriate treatment as early as possible.
- To our knowledge there have been no prospective studies investigating the incidence and predictive factors of bone metastasis and SREs in pts. with advanced lung cancer
- It is worthwhile investigating how therapeutic intervention such as chemotherapy, radiotherapy and bisphoshonate could affect the clinical course of lung cancer pts. with bone metastasis and development of SREs

PURPOSE

The aim of this study is to prospectively investigate the following items in pts. with advanced lung cancer.

1) Incidence of bone metastasis (BM) at initial diagnosis in pts. with small cell lung cancer (SCLC) and stage IV non-small cell lung cancer (NSCLC) , and time interval of developing BM in pts. with SCLC and stage IIIB lung cancer who have no BM at initial diagnosis

2) Time interval between BM and development of SREs, and incidence and types of SRE

3) Predictive factors of BM and SRE

MATERIALS AND METHODS

Definition of SRE is 1) pathologic fracture, 2) radiation to bone lesion, 3) surgery to bone, 4) spinal cord compression, and 5) hypercalcemia of malignancy.

Staging of lung cancer required CT scan of the chest and upper abdomen, bone scan or PET scan, and CT or MRI scan of the brain. Pts. were closely monitored every 4 weeks to see if they developed SREs.

During the follow up period the pts. underwent CT scan of the chest and upper abdomen every 4 weeks, CT or MRI scan of the brain and bone scan or PET scan every 6 months. A QOL questionnaire was carried out at enrollment, 3 months and 12 months. Treatment for lung cancer and use of zoledronate were at the discretion of the investigator (Table 1).

Eligibility Criteria

Inclusion criteria

1. newly diagnosed SCLC in all stages and NSCLC in stage IIIB or stage IV
2. age ≥ 20 years
3. able to reply to QOL questionnaire
4. written informed consent
5. treatment for lung cancer and use of zoledronate were at the discretion of the investigator

Exclusion criteria

1. pts. who were judged to be inappropriate for enrollment by the investigator

Table (1) Schedule of examination

Visit	0	1	2	3	4	5	6	7	8	9－12
	Enrollment	1month	2months	3months	4months	5months	6months	9months	12months	24months
Allowance	≤1month	±2wks	±2wks	±2wks	±2wks	±2wks	±2wks	±6wks	±6wks	±6wks
Bone scintigram or PET	○						★		○	
X-ray（DV・L-spine）	○									
Chest CT	○(pleura)			☆			☆	☆	☆	
Patient background	○									
P.S.	○	○	○	○	○	○	○	○	○	
height	○						★			
weight	○	○	○	○	○	○	○	○	○	
Blood biochemistry	○	○	○	○	○	○	○	○	○	
Tumor marker	○	○	○	○	○	○	○	○	○	Repeat between 7and 8
Bone marker（blood・urine）	○									
Bone metastasis	○	○	○	○	○	○	○	○	○	
Metastasis extra-bone	○	○	○	○	○	○	○	○	○	
Bisphosphonate	○	○	○	○	○	○	○	○	○	
Bone Pain	○	○	○	○	○	○	○	○	○	
Analgesic use	○	○	○	○	○	○	○	○	○	
SRE	○	○	○	○	○	○	○	○	○	
QOL・ADL	○			☆	4 wks after SRE(±2wks)					
Outcome	On demand									

★：±4wks ★：±6wks

Total Enrollment: 277 patients
- Entry period: April 2007 to December 2009
- Participating institution: 12
- Follow up：until December 2011
- Exclusion：delayed registration 2
  not eligible (stage IIIA NSCLC) 1

Analysis： 274 patients
- SCLC 77
- NSCLC
  - Stage IIIB 73
  - Stage IV 124
  - Termination 249
  - ✓ 2yr. completion 64
  - ✓ death 112
  - ✓ referred to other hospital 65
  - ✓ patient refusal 3
  - ✓ others 5
  - Under follow-up 25

Follow-up duration(median): 12.7 months [range 0-27.4]

Analysis for time data： 272 pts.
- 2 pts. were excluded due to missing data.

RESULTS

◆ Two hundred and seventy four pts. were enrolled in the study between Apr. 2007 and Dec. 2009 from 12 institutions (Table 2).

◆ Median age was 68 years, small cell/non-small cell=77/197, IIIB/IV=73/124, M/F=193/81, PS 0/1/2/3-4=76/171/23/4. Median follow up time was 10.3 months (0-27.2 months).

◆ Seventy eight of 124 pts. with stage IV NSCLC (48%) already had BM at the time of enrollment (Fig. 1).

◆ Twenty four of 78 pts. with known BM (31%) had some kind of SRE concomitantly. Additional 11 pts developed SRE during follow up time and the total incidence of SRE was 45%.

◆ Thirty four of 196 pts. without initial BM (17%) developed bone metastases, and 15 of these 34 pts developed SREs during the follow up period

◆ The type of SRE was radiation to bone 15.7%, pathologic fracture 4.7%, hypercalcemia 2.2% and spinal cord compression 1.1% (Table 3)

◆ Multivariate analysis by Cox regression model showed that factors predicting subsequent bone metastasis at enrollment were NSCLC, stage IV, PS >1, LDH and bone alkaline phosphatase (Table 4)

◆ Multivariate analysis by Cox regression model showed that factors predicting subsequent SRE at enrollment were NSCLC, stage IV and age < 64 (Table 5)

Table (2) Patients characteristics at enrollment

		NSCLC		SCLC		Total
		Stage IIIB	Stage IV	LD	ED	
n		73	124	45	32	274
Gender（Male/Female）		57/16	79/45	57 /20		193/ 81
Age（Median〔Range〕）		69.0 〔35-86〕	67.0 〔41-89〕	69.0 〔45-82〕		68.0 〔35-89〕
PS (ECOG)	0	22 (30.1)	31 (25.0)	23 (29.9)		76 (27.7)
	1	43 (58.9)	82 (66.1)	46 (59.7)		171 (62.4)
	2	7 (9.6)	8 (6.5)	8 (10.4)		23 (8.4)
	≥3	1 (1.4)	3 (2.4)	0 (0)		4 (1.5)
Bone metastasis	-	73 (100.0)	65 (52.4)	58 (75.3)		196 (71.5)
	+	0	59 (47.6)	19 (24.7)		78 (28.5)
SRE	-	73 (100.0)	104 (83.9)	73 (94.8)		250(91.2)
	+	0	20 (16.1)	4 (5.2)		24 (8.8)

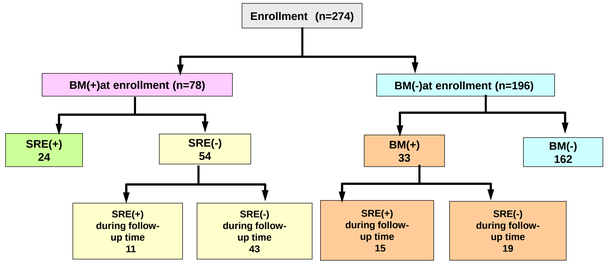

Fig. (1) Tree diagram of enrolled patients

CONCLUSIONS

❖ The incidence of BM at initial diagnosis was 50% in pts. with stage IV lung cancer and was higher than initially expected

❖ Various SREs developed in 18 % of all pts. during follow up time

❖ Forty percent of pts. enrolled in the study had bone metastasis and half the pts. who had developed bone metastasis had SRE during follow up time

❖ Multivariate analysis revealed that factors predicting bone metastasis were NSCLC, stage IV, PS ≥1, LDH and bone alkaline phosphatase, and factors predicting SRE were NSCLC, stage IV and age ≤ 64

❖ Quality of life assessment and other therapeutic factors affecting bone metastasis and SREs will be reported next year

Table (3) Incidence and type of SRE (n=274)

	All SRE		New SREs during follow up		Total	
	n	%	n	%	n	%
Any SRE	24	8.8	26	9.5	50	18.2
Pathologic fracture	9	3.3	4	1.5	13	4.7
Radiation to bone lesion	22	8	21	7.7	43	15.7
Surgery to bone	0	0	0	0	0	0
Spinal cord compression	2	0.7	1	0.4	3	1.1
Hypercalcemia of malignancy	1	0.4	5	1.8	6	2.2

Table (4) Cox regression for BM incidence <multivariable analysis>

Factor	n	Events	HR	(95% CI)	p value
NSCLC/SCLC	271	111	**2.23**	**(1.38-3.60)**	**0.001**
NSCLC (stage IV/stage IIIB)	**271**	**111**	**7.13**	**(3.61-14.10)**	**<.0001**
Gender (female/male)	271	111	1.03	(0.67-1.57)	0.895
Age (≥65 / ≤64)	**271**	**111**	0.74	(0.49-1.11)	0.146
PS (>1 / 0)	**271**	**111**	**1.70**	**(1.03-2.80)**	**0.037**
LDH [1000 U]	**271**	**111**	**2.72**	**(1.23-6.02)**	**0.014**
Alb [g/dL]	271	111	0.76	(0.51-1.13)	0.175
Ca [mg/dL]	271	111	0.91	(0.69-1.19)	0.486
PTHrP [pmol/L]	264	109	0.90	(0.74-1.10)	0.308
BALP [100U/L]	**267**	**109**	**1.94**	**(1.13-3.33)**	**0.016**
NTx [1000nmolBCE/mmolCRE]	266	109	0.82	(0.31-2.14)	0.688

Table (5) Cox regression for SRE incidence <multivariable analysis>

Factor	n	Events	HR	(95% CI)	p value
NSCLC/SCLC	**247**	**50**	**2.82**	**(1.33-5.97)**	**0.007**
NSCLC (stage IV/stage IIIB)	**247**	**50**	**4.48**	**(1.84-10.94)**	**0.001**
Gender (female/male)	247	50	0.82	(0.42-1.58)	0.545
Age (≥65 / ≤64)	**247**	**50**	**0.44**	**(0.24-0.78)**	**0.005**
PS (>1 / 0)	247	50	1.23	(0.60-2.52)	0.576
LDH [1000 U]	247	50	1.57	(0.46-5.32)	0.469
Alb [g/dL]	246	50	0.64	(0.38-1.09)	0.101
Ca [mg/dL]	247	50	0.88	(0.61-1.27)	0.500
PTHrP [pmol/L]	240	50	0.96	(0.75-1.23)	0.742
BALP [100U/L]	243	50	1.17	(1.89-1.54)	0.248
NTx [1000nmolBCE/mmolCRE]	242	50	0.79	(0.23-2.71)	0.703

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