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Original Paper

Effect on Prognosis of Bone Marrow Infiltration Detected by Magnetic Resonance Imaging in Small Cell Lung Cancer

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The staging system of limited disease (LD) and extensive disease (ED) is widely used and has been shown to provide useful prognostic information in cases of small cell lung cancer (SCLC). However, accurate examinations are necessary for correct staging. In this report, we evaluated the clinical usefulness of magnetic resonance imaging (MRI) of bone marrow in SCLC. 37 patients with LD by standard staging and 41 with ED were examined with bone marrow MRI. Results of bone marrow MRI did not influence the choice of treatment in patients with LD. For subsequent analysis, patients with LD were divided into two groups: patients in whom bone marrow infiltration was detected with MRI (MRI-positive LD group) and those in whom it was not (MRI-negative LD group). Focal or diffuse metastases to bone marrow were detected with MRI in 46% (36/78) of all patients and 35% (13/37) of LD patients. The response rates to treatment in patients with MRI-positive LD were lower than those in patients with MRI-negative LD ($P = 0.006$). The survival of patients with MRI-positive LD was worse than that of MRI-negative LD (generalised Wilcoxon test: $P = 0.0157$), and closer to that of ED. Multivariate analyses using a Cox model that included the result of bone marrow MRI, performance status, chemotherapy regimen, radiotherapy and serum lactose dehydrogenase (LDH) level showed that the result of bone marrow MRI remained a prognostic factor in SCLC patients with limited disease. Bone marrow examination with MRI is useful for better staging of SCLC. According to our analysis of response rates and survival, MRI-positive LD should be considered a type of ED. © **1997 Elsevier Science Ltd.**

Key words: small cell lung cancer (SCLC), magnetic resonance imaging (MRI), bone marrow metastasis, staging, prognosis
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INTRODUCTION

SMALL CELL lung cancer (SCLC) accounts for 25% of malignant lung tumours and differs from other types of lung cancer by its early and widespread dissemination and pronounced sensitivity to chemotherapy and radiotherapy. The staging system [1, 2] of SCLC consists of limited disease (LD) and extensive disease (ED) and has been shown to provide valuable prognostic information. For accurate staging, all metastatic lesions must be detected. Although bone marrow is a frequent metastatic site in SCLC [3], the reported rates of detection with biopsies of bone marrow involvement range from 10 to 20% [4–7]. Because of the difficulty of evaluating multiple bone marrow sites with biopsy, a more sensitive and comprehensive method of examination is required [8]. Magnetic resonance imaging (MRI) has been reported to be an effective alternative for bone marrow examinations [9–11]. Previous reports [12–14] suggest that low-intensity lesions on T1-weighted images and high-intensity or iso-intensity lesions on T2-weighted images in bone marrow indicate infiltration of cancer. We have already reported the clinical utility of MRI in detecting bone marrow involvement in patients with SCLC [9]. In the present report, we evaluated the efficacy of MRI in detecting bone marrow

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Table 1. *Therapy*

	LD				ED ($n = 41$)	
	BM MRI-negative ($n = 24$)		BM MRI-positive ($n = 13$)			
	No.	Percentage	No.	Percentage	No.	Percentage
Chemotherapy						
with platinum	22	92	11	85	25	61
(platinum+etopside)	18	75	8	62	19	46
without platinum	2	8	2	15	9	22
Radiation	17	71	8	62	9	22

With platinum: cisplatin or carboplatin + etoposide, cisplatin + irinotecan, cisplatin + cyclophosphamide + doxorubicin + etoposide. Without platinum: cyclophosphamide + doxorubicin + vincristine, cyclophosphamide + doxorubicin + vincristine + etoposide
BM, bone marrow.

involvement and investigated the prognostic significance of detected lesions in patients with SCLC.

PATIENTS AND METHODS

78 patients with SCLC were admitted to Osaka Medical Center for Cancer and Cardiovascular Diseases from January 1990 to January 1996 and underwent both staging examinations and MRI examinations of bone marrow. The diagnosis of SCLC was made histologically or cytologically with specimens of the primary lesion obtained at transbronchial biopsy or percutaneous aspiration biopsy. Standard staging procedures included chest radiography, chest computed tomography (CT), brain CT or MRI or both, abdominal ultrasonography or CT or both, radionuclide bone scans and bone marrow aspiration biopsy of the sternum. On the basis of standard staging methods without bone marrow MRI, 37 of the 78 patients were classified as having LD and 41 as having ED. The MRI examinations were performed, as previously reported [9], with a 1.5 T whole-body superconducting magnet and a body coil. Both T1- and T2-weighted images of the sternum, spine, pelvis and proximal femur were routinely obtained. Sagittal views were obtained of the sternum and the cervicothoracic spine; coronal views were obtained of the lumbar spine, pelvis and proximal femur. On the basis of standard age-related patterns of haematopoietic and fatty bone marrow distribution in the axial skeleton [15], metastasis was judged to be present when lesions showed low intensity on T1-weighted images and showed iso or high intensity on T2-weighted images. In cases in which the pattern of abnormal intensity was difficult to judge, T1-weighted images were also obtained after intravenous administration of gadopentate dimeglumine (Gd-DTPA; 0.1 mmol/kg) for contrast enhancement. When lesions in the bone marrow showed enhancement with Gd-DTPA, bone marrow involvement was diagnosed.

Patients received chemotherapy with or without radiotherapy (Table 1). Results of bone marrow MRI did not influence the choice of treatment in patients with LD. Chemotherapy alone or chemotheropy with concurrent or sequential irradiation of primary sites were administered. The majority of these patients were allocated to one of several independent clinical trials, in which the regimens such as CAV (cyclophosphamide, doxorubicin and vincristine), PE (cisplatin and etoposide), CODE (cisplatin, cyclophosphamide, doxorubicin and etoposide), CAVE (cyclophosphamide, doxorubicin, vincristine and etoposide) and cisplatin and irrinotecan were used as chemotherapy. Most patients received platinum-based chemotherapy. Irradiation of the primary lesion was performed in LD patients if possible. In ED, only the patients in whom chemotherapy achieved complete remission or who had single metastatic lesion underwent irradiation of the primary lesion.

Patients with LD by standard staging were divided into two groups: those in whom bone marrow infiltration was detected with MRI (MRI-positive LD) and those in whom it was not detected (MRI-negative LD). The response to treatment and survival of the two groups were compared. The response to chemotherapy was determined with World Health Organisation criteria for reporting results of cancer treatment.

Response to treatment was analysed by Chi square test; haematological and biochemical values in peripheral blood were analysed by Student's *t*-test; survival curves were prepared by Kaplan–Meier methods and analysed by generalised Wilcoxon test. Multivariate analyses were performed using a Cox's proportional hazard model.

RESULTS

In 36 (46%) of the 78 patients, 13 (35%) of 37 LD patients and 23 (56%) of 41 ED in the standard staging, focal or diffuse metastatic lesions were detected with MRI (Table 2).

Metastases were detected in a much higher percentage of cases with bone marrow MRI (46.2%) than with other staging methods (12–19%). Therefore, bone marrow, when examined with MRI, was the most frequent metastatic site among the areas examined for the staging (Table 2).

Table 2. *The detection rate of metastasis with standard staging methods and bone marrow MRI*

	No.	Percentage
Brain CT and/or MRI	12	15
Chest CT	9	12
Abdominal US and/or CT	13	17
Bone scintigram	15	19
Bone marrow biopsy	11	14
Bone marrow MRI	36	46
LD ($n = 37$)	13	35
ED ($n = 41$)	23	56

MRI, magnetic resonance imaging; CT, computed tomography; US, ultrasonograpy; LD, limited disease; ED, extensive disease.

Table 3. The response rate to the treatment

		CR (%)	PR (%)	NC (%)	PD (%)	RR (%)
LD						
negative BM MRI	($n=24$)	4 (17)	20 (83)	0	0	24 (100)*
positive BM MRI	($n=13$)	1 (8)	9 (69)	3 (23)	1 (8)	10 (77)*†
ED	($n=41$)	2 (5)	21 (51)	5 (12)	12 (29)	23 (56)†

*$P=0.0066$; †$P=0.3575$. CR, complete response; PR, partial response; NC, no change; PD, progressive disease; RR, response rate; BM, bone marrow.

It is noteworthy that the detection rate of metastasis with bone marrow aspiration biopsy was only 14%. In 36 patients in whom bone marrow metastasis was detected with MRI, bone marrow aspiration biopsy was negative in 25 (69%). In contrast, only 2 (18%) of 11 patients in whom metastasis was detected with bone marrow biopsy were judged MRI-negative: in 1 patient the lesion was a direct invasion to the bone.

Of 13 patients in whom bone marrow metastasis was detected with MRI but not with initial bone scintigraphy, new lesions appeared on follow-up bone scintigraphy in 11 patients. In 8 (72.8%) of these 11 patients, new lesions appeared at the same sites where lesions had been detected on initial MRI. In the other 3 patients, new bone lesions appeared in areas MRI was not performed, including the ribs and skull (data not shown).

Haematological and biochemical values in peripheral blood were compared in MRI-negative and positive-LD patients to see whether a correlation existed in the rate of detection of bone marrow involvement with MRI. There were no statistically significant differences in white blood cell (WBC) and platelet counts, lowest WBC and platelet counts, lactic dehydrogenase (LDH) values and alkaline phosphatase values (data not shown).

The rates of response and complete response to treatment in cases of MRI-positive LD (77% and 8%, respectively) were lower than those in cases of MRI-negative LD (100% and 17%, respectively, Table 3). The difference in the response rates was statistically significant ($P=0.006$).

The survival of patients with MRI-positive LD was statistically significantly worse in the generalised Wilcoxon test than that of MRI-negative LD and closer to that of ED (Figure 1). The median survival time (MST) of patients with MRI-positive LD was shorter than that of patients with MRI-negative LD. Additionally the 1-year survival rate of patients with MRI-positive LD was lower than that of patients with MRI-negative LD. Thus, the lack of MRI evidence of metastasis in bone marrow is related to a better survival in LD. The treatment received did not differ significantly between the groups (Table 1). MRI results remained significantly associated with survival of LD patients in a Cox model that included chemotherapy regimens (platinum-based versus non-platinum-based), irradiation for primary

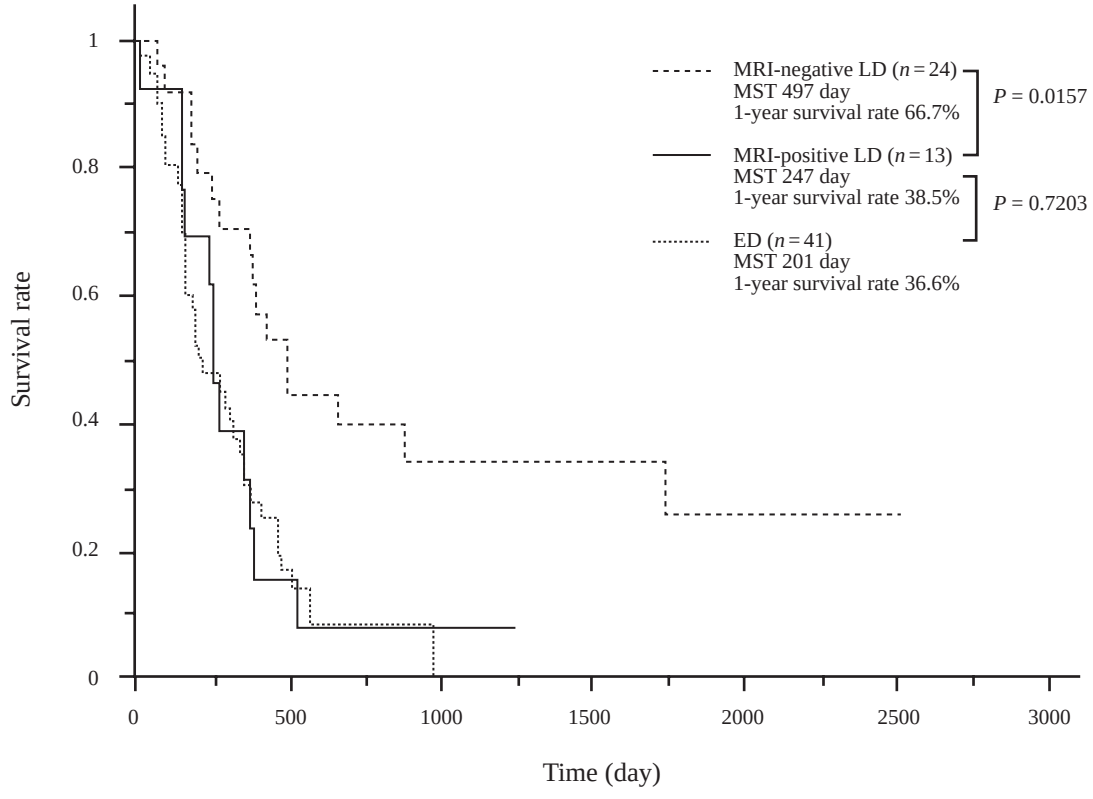

Figure 1. Survival after the start of initial therapy (MST, median survival time; LD, limited disease; ED, extensive disease).

Table 4. Multivariate analyses of factors predicting survival

Factor	Hazards ratio	95% Confidence interval	*P*
PS(0, 1)	0.547	0.184–1.628	0.278
Treatment			
platinum-based	0.446	0.130–1.533	0.200
irradiated	0.402	0.147–1.096	0.075
Positive bone marrow MRI	5.175	1.943–13.784	0.001
Normal LDH	0.120	0.034–0.418	0.001

Variables are ECOG performance status (0–1 versus 2–4); chemotherapy (platinum-based versus non-platinum-based); radiation (irradiated primary lesion versus non-irradiated); bone marrow MRI (negative versus positive); serum LDH level (normal versus high).

lesions, performance status (ECOG 0–1 versus 2–4) and serum LDH level ($P = 0.001$ Table 4).

DISCUSSION

Bone marrow metastasis is detected by biopsy in 10–20% of patients with SCLC at the time of initial diagnosis [4–7]. Although several authors have reported increased sensitivity with monoclonal antibodies [16, 17], this procedure is limited because material can be obtained from only one or two sites.

MRI has been reported to be useful for bone marrow examination [18–20]. Carney and associates [10, 21] reported that MRI could detect metastatic lesions in bone marrow in SCLC. In a previous study, we showed that detection of bone marrow metastasis by MRI was superior to that by either bone marrow biopsy or bone scintigraphy, suggesting that MRI examination would have a significant influence on the staging of SCLC. We obtained specimens of bone marrow from cases in which abnormal MRI findings indicated metastasis. These specimens showed histological involvement of SCLC [22]. Patients positive for bone marrow infiltration by the MRI technique but not by bone marrow aspiration proved not to be false–positive cases in lymphoma as reported by Shields and associates [23]. These results indicate that the criteria we adopted in this study to diagnose MRI lesions in bone marrow are valid.

We showed in the present study that 35% of patients with LD by standard staging techniques were found to have ED when bone marrow MRI was also used for staging. Tritz [24] reported that bone marrow was the only site of metastatic involvement in only 2–4% of patients examined with aspiration biopsy. Østerlind [25] reported that bone marrow metastases were detected in 40 (4.2%) of 942 SCLC patients who had normal LDH values and that 31 (78%) of these patients had metastases in another organ which could be detected by other methods. These results suggest that the value of routine use of bone marrow examination in SCLC should be questioned [26, 27]. However, our study clearly shows that it is important to evaluate bone marrow with MRI in SCLC. MRI showed the bone marrow to be the only site of metastasis in 13 (17%) of 78 patients.

The relationship between bone marrow involvement and elevated biochemical parameters has been examined. Increased levels of LDH have been reported [28–30] in SCLC patients with bone marrow involvement. However, in our study, there were no significant differences in biochemical (LDH, ALP) and haematological parameters (WBC and platelet counts, lowest WBC and platelet counts) between patients with MRI-negative and MRI-positive LD. Levels of LDH are known to correlate with the degree of bone marrow involvement. In most cases, the metastatic area is localised and involves a relatively small amount of the bone marrow. This limited involvement may be one reason we were unable to detect a difference in LDH values between patients with MRI-negative and MRI-positive LD. MRI appears to detect lesions of bone marrow metastasis earlier than does bone marrow biopsy.

New lesions on bone scintigraphy during the follow-up period appeared with high probability at the same sites where lesions were found on initial MRI (data not shown). Skeletal scintigraphy is especially sensitive for abnormalities of the cortical bone and is considerably less sensitive for abnormalities of the marrow. This difference suggests that these new lesions on bone scintigraphy are due to direct invasion of the cortical bone from bone marrow metastases detected with initial MRI.

The results of bone marrow MRI may predict clinical course. The rates of response and complete response of patients with MRI-positive LD were lower than those of patients with MRI-negative, but no difference existed between MRI-positive LD and ED. The high response rate observed in MRI-negative LD patients is surprising. The high response rate remained statistically significant when compared in the patients who received platinum-based regimens ($P = 0.034$), which is known to be more effective than non-platinum-based therapy. The difference of response rate cannot be ascribed to the difference of chemotherapy regimens. As shown in Table 1, the ratio of irradiated patients was almost the same between MRI-negative and MRI-positive LD, suggesting that the influence of radiation on response rate was also negligible. The patients with MRI-negative LD have earlier disease than those with MRI-positive LD and, therefore, the appearance of clones resistant to the treatment might be minimal in the tumour in MRI-negative LD. The survival of patients with MRI-positive LD was closer to that of patients with ED rather than to patients with MRI-negative LD. Furthermore, patients with MRI-positive LD had a worse prognosis as indicated by a shorter MST and lower one-year survival rate. When PS, treatment and serum LDH level were taken into consideration, the negative result of bone marrow MRI remained predictive of better survival of LD patients. Together, these results suggest that bone marrow MRI is a useful technique for staging of SCLC and that patients in whom bone marrow infiltration is detected with MRI should be considered to have ED. A larger study will be necessary to confirm these results.

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