

## BONE MARROW EXAMINATION IN SMALL CELL LUNG CANCER — WHEN IS IT INDICATED?

J. FELIU, M. GONZÁLEZ BARÓN, A. ARTAL, A. ORDÓÑEZ, I. CEBREIROS, G. MARTÍN, P. GARRIDO,  
I. CHACÓN and J. M. MONTERO GARCÍA

### Abstract

To assess the usefulness of bone marrow (BM) examination performed as part of the staging procedure in SCLC, 137 patients with this neoplasm were studied. At diagnosis, BM was infiltrated in 23 patients (17%) and in 5 of them (22%) it was the only metastatic site. BM examination changed the previously given stage in 9% of the patients who were supposed to have limited disease before this test was performed. BM involvement correlated with a higher frequency of bone ( $p < 0.05$ ) and liver ( $p < 0.01$ ) metastasis. Correlations were found neither with blood or serum biochemistry disturbances nor with postchemotherapy haematologic toxicity. The BM positive patients had a survival rate similar to those with extensive disease but without BM infiltration. We conclude that BM examination should be performed only when no other metastatic sites have been found after a complete staging study.

*Key words:* Small cell lung cancer, bone marrow metastasis, staging, prognosis.

Bone marrow (BM) examination is usually included in the initial routine work-up performed to assess the extent of small cell lung cancer (SCLC). In various series, BM metastasis has been described in 6–45% (1, 2). However, during the past few years the routine use of this test has been questioned, and several authors have found only a small percentage of patients (0–4%) in whom the stage or the treatment changed as a result of BM examination (3–5). Besides, when BM is infiltrated by SCLC cells neither prognosis nor tolerance of chemotherapy seems to be modified (4, 5).

In SCLC, in contrast to most solid tumours, BM involvement is rarely associated with altered blood count or immature cells in peripheral blood (4–6). Nevertheless, a relationship has been reported with elevated serum lactic

dehydrogenase (LDH) (7, 8), alterations of other biochemical parameters (5) or bone metastasis (8, 9).

The aim of our study was to assess the usefulness of BM examination in staging SCLC, to identify factors that may predict BM infiltration and to determine its prognostic influence.

### Material and Methods

BM of 137 patients consecutively diagnosed as SCLC was examined between January 1984 and January 1989. The sample was obtained through unilateral biopsy of the posterior iliac crest with a Jamshidi needle, using the technique of Jamshidi & Swain (10).

In every case, BM aspirate and peripheral blood smear were obtained.

The staging procedure included blood count, serum biochemistry as detailed below, chest roentgenography, thoracic and abdominal CT scans, fiberoptic bronchoscopy and radionuclide bone scan. Cranial CT was made when neurological symptoms existed.

Limited disease (LD) was defined as tumour confined to one lung, mediastinum and/or supraclavicular nodes (ipsi- or contralateral). Otherwise, the disease was considered as extensive (ED).

All patients received combination chemotherapy, but the schemes varied over the study period. Between January 1984 and January 1987, seventy-nine patients received 9 courses of etoposid, doxorubicin and cyclophosphamide.

Submitted 5 July 1990.

Accepted for publication 31 October 1990.

**Table 1**

Results of BM biopsy and aspirate in 23 patients with BM infiltration

	Biopsy + Aspirate -	Biopsy - Aspirate +	Biopsy + Aspirate +
Number	7	1	15
Percentage	30	4	66

From February 1987 to January 1989, fifty-eight patients were given 9 courses of alternating chemotherapy with ifosfamide-doxorubicin-vincristine and carboplatin-cyclophosphamide-etoposid. In LD, thoracic radiotherapy was added and, if the patient reached a complete remission, also prophylactic cranial radiotherapy.

The following data were analyzed: haemoglobin, leukocytes with differential count, platelets, lactate dehydrogenase (LDH), glutamic oxalacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), alkaline phosphatase (AP), gammaglutamil transpeptidase (SGGT), uric acid and sodium values; leukoerythroblastic reaction (defined as presence of myeloid immature or erythroid precursors in the peripheral); hematological toxicity graded according to the WHO scale; dose of cytostatic drugs administered with respect to the initially calculated; length of bone cylinder obtained; other metastatic sites and survival.

The Mann-Whitney non-parametric test was used for comparison of quantitative variables and  $\chi^2$ -test for qualitative ones.

Survival curves were made by the method of Kaplan & Meier (11) and log-rank test (12) was used to analyze differences.

### Results

BM involvement was found in 23 of the 137 patients (17%). Biopsy was positive in 22 (96%) and aspirate in 16 (70%) (Table 1). Mean length of the bone cylinder was  $20.3 \pm 8.8$  mm in patients with BM involvement and  $18.1 \pm 6.6$  mm in patients without infiltration. This difference was not significant.

Among the 59 patients with initially LD (43%), BM biopsy changed the stage in 9% (Table 2), and BM was the only metastatic site in 5 patients (4%).

**Table 2**

Frequency of BM involvement in 137 patients with SCLC

	No. of patients	BM infiltrate
Overall results	137	23 (17%)
Limited disease (*)	59	5 (9%)
Extended disease (**)	78	18 (23%)

\*Before result of BM biopsy.

\*\*Patients with BM as the only metastatic site not included.

**Table 3**

Laboratory test results according to presence and absence of BM infiltration. None of the differences is statistically significant

Parameter (M $\pm$ SD)	Non-involved BM	Involved BM
Haemoglobin (g/l)	136 $\pm$ 21	139 $\pm$ 16
Leukocytes $\times 10^9/l$	7.76 $\pm$ 2.36	7.58 $\pm$ 3.50
Neutrophiles $\times 10^9/l$	5.21 $\pm$ 2.06	5.10 $\pm$ 2.65
Lymphocytes $\times 10^9/l$	1.56 $\pm$ 0.68	1.59 $\pm$ 0.69
Platelets $\times 10^9/l$	269 $\pm$ 126	341 $\pm$ 300
LDH (UI/l)	350 $\pm$ 240	290 $\pm$ 174
SGOT (UI/l)	41.6 $\pm$ 18.7	42.8 $\pm$ 26.0
SGPT (UI/l)	54.6 $\pm$ 18.6	40.7 $\pm$ 12.6
SGGT (UI/l)	90.5 $\pm$ 34.1	84.1 $\pm$ 54.7
AP (UI/l)	91.4 $\pm$ 32.3	97.8 $\pm$ 56.7
Albumin (g/l)	3.91 $\pm$ 0.3	3.96 $\pm$ 0.4
Sodium (mmol/l)	137 $\pm$ 4.3	138 $\pm$ 3.0
Uric acid (mmol/l)	0.34 $\pm$ 0.04	0.35 $\pm$ 0.06

Table 3 shows the values of the laboratory tests performed in patients with and without BM infiltration. No significant differences could be found between the groups. A leukoerythroblastic reaction was found in 4 patients with BM involvement and in 12 with normal BM; the difference was not statistically significant.

Serum LDH was elevated in 70% of the patients with BM metastasis and in 52% of those without BM spread and this difference was not statistically significant.

Liver ( $p < 0.01$ ) and bone ( $p < 0.05$ ) metastases were found more frequently in patients with BM involvement, while no significant relation was found with metastases in other sites (Table 4).

Elevated serum LDH and/or pathological radionuclide bone scan were found in 78% of the patients with BM involvement and 57% of the patients without it; the difference was not significant.

The proportion between administered and calculated doses of chemotherapy was compared; 69% of patients with BM involvement and 78% of patients without such involvement received over 75% of the calculated dose. This difference was not statistically significant.

Table 5 shows haematological toxicity in patients with and without BM involvement. Toxicity was similar in both groups. There was one toxic death among patients with BM infiltration and 4 in the non-involved group. The

**Table 4**

Relationship between BM infiltration in SCLC and other distant metastases

Metastatic site	BM involved (n = 23)	BM non-involved (n = 114)	Statistical significance
Bone	10	25	$p < 0.05$
Liver	12	26	$p < 0.01$
CNS	2	9	NS
Other	3	18	NS

Table 5

*Haematological toxicity and BM metastases*

Parameter	BM involved (181 courses)		BM non-involved (1014 courses)	
	Toxicity grades		Toxicity grades	
	1-2	3-4	1-2	3-4
Haemoglobin	63 (35%)	16 (9%)	426 (42%)	71 (7%)
Leukocytes	61 (34%)	45 (25%)	304 (30%)	294 (29%)
Neutrophiles	52 (29%)	37 (20%)	263 (26%)	223 (22%)
Platelets	28 (15%)	13 (7%)	121 (12%)	61 (6%)

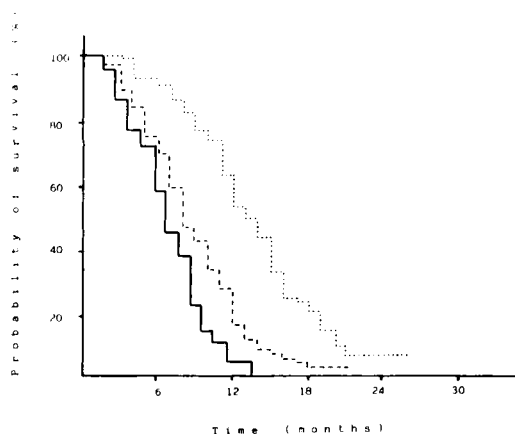


Figure. Probability of survival in patients with small cell lung cancer as related to extent of disease. There was a significant difference between the survival of patients with limited disease (LD) and extended disease (ED) without bone marrow (BM) involvement ( $p < 0.001$ ). No significant difference was found between ED without BM involvement and ED with BM involvement ( $p > 0.05$ ). ···· LD ( $n = 54$ ); --- ED without BM involvement ( $n = 60$ ); — ED with BM involvement ( $n = 23$ ).

survival of patients with BM infiltration was similar to the survival of patients with other metastatic sites and, as expected, shorter than the survival of patients with limited disease ( $p < 0.001$ ) (Figure).

### Discussion

In previously published series BM involvement at diagnosis has been reported in 6–45% of patients with SCLC (1, 2). In our series, the frequency was 17%.

Initially, some authors suggested that BM aspirate was more accurate than biopsy in revealing tumour cells in BM (13, 14). However, in our study biopsy revealed 96% of the BM involvement and was much more sensitive than aspirate. Our observations agree with those of the majority of authors (4, 6, 15) and we consider aspiration only as an adjunct to biopsy. Both bone cylinder length (16) and surface area of the examined BM (4) have been believed

to influence the detection of BM involvement. In order to achieve maximal yield some investigators routinely perform two biopsies on the same side and have reported a 24% rate of positive findings (15). Other authors have performed bilateral biopsies in both iliac crests and Hirsch et al. (14) reported that this procedure gave a yield about 25% higher than unilateral examination. However, the difference in yield of unilateral and bilateral biopsy was very small in a study by Kelly et al. (17), and so these authors do not recommend the bilateral procedure. In our study the bone cylinders were slightly longer in patients with BM involvement than in the non-involved group, but the difference was not significant.

Recently it has been stressed that patients with BM involvement have a higher overall rate of metastasis and BM as the only metastatic site has been reported in 0–5% of the patients only (3–5, 7, 18, 19). Accordingly, some authors do not advise the routine use of BM examination (3–5, 19). In our series, BM examination changed the stage in only 4% of all patients, and increased in 9% of the patients initially classified as LD. This rate is similar to other series (3.5–12%) (1, 4–6, 18, 20–22) and it should probably have been somewhat higher if bilateral biopsy had been performed. We conclude that BM biopsy for staging is justified in this group.

Several authors have tried to define some features that could help to identify patients with involved BM (4–6). Anemia (4–6) and thrombocytopenia (4) have in some studies been correlated with BM infiltration, but our data, as the data of some other authors (5, 8, 9) do not confirm that relation. At all events, this correlation is not strong enough to be of practical value (4, 6). A leucoerythroblastic reaction may suggest BM infiltration, but its frequency is too low to be considered useful (9.5–37%) (4, 6). LDH is the variable most often mentioned as correlated with BM involvement. Several authors have found significantly increased LDH in patients with BM metastasis (4, 5, 7, 8) and some authors have even suggested that BM biopsy can be dispensed with if LDH is normal (7). In our study we did not find a significant difference between

LDH in patients with and without BM involvement. In fact, 40% of our BM-positive patients had normal serum LDH. In agreement with some other authors (23, 24) we are of the opinion that LDH values cannot serve as guidance to whether BM biopsy should be done or not.

To increase the predictive value of LDH, it has been used together with AP (4), SGOT, SGPT, albumin and sodium (5) or radionuclide bone scan (8). In our series, BM infiltration was only related to the presence of bone metastases as detected with scintigraphic studies. However, when bone scans and LDH values were analyzed together we found that 5 of 23 patients (21%) with BM involvement had normal scans and LDH values. Thus we found no variables useful for the identification of patients with BM involvement prior to the biopsy.

Some authors use results of BM examinations not only for staging but also as a prognostic factor (25). It has been reported that patients with BM involvement have a shorter survival than patients with other metastatic sites (9). The poor prognosis has been found to be independent of the dose of cytotoxic drugs received (9). In our series, patients with BM infiltration had slightly better survival than patients with other metastatic sites, but the difference was not significant. This might be related to the relatively low number of patients in our study. However, some other authors have also failed to find a survival difference between these two groups of patients (4-6, 17).

The declining role of BM examination in SCLC can partly be explained by the introduction of thoracic and abdominal CT scans, which were not available in the early 1970s when BM examination was first described as an evaluable method for detection of metastatic spread in SCLC. However, a distinctive merit of this procedure is that a positive finding means histological proof of dissemination. Interpretation of the other tests used for staging of lung cancer, especially bone scan, may be less simple.

Most new cases of lung cancer will in future be found in the Third World, where resources are limited and expensive and sophisticated technology such as CT is not often available. Here BM examination has the advantage of being cheap, simple, and possible to perform without delay.

The results of our study, lead us to believe that BM biopsy should be routinely performed only when no metastases have been found by other methods.

*Corresponding author:* Dr J. Feliu, Servicio de Oncología Médica (H. General), Hospital La Paz, Castellana 261, E-28046 Madrid, Spain.

#### REFERENCES

- Giaccone G, Ciuffreda L, Donadio M, et al. Bone marrow evaluation in small cell carcinoma of the lung. *Acta Oncol* 1987; 26: 185-8.
- Hansen HH, Muggia FM, Selawry OS. Bone-marrow examination in 100 consecutive patients with bronchogenic carcinoma. *Lancet* 1971; 2: 443-5.
- Manegold C, Krempien B, Bulzeck H, Drings P. Value of bilateral iliac crest needle biopsy for pretherapeutic tumor staging of bronchogenic carcinomas. *Oncology* 1989; 46: 226-9.
- Campling B, Quirt I, De Boer G, Felld K, Shepherd FA, Evans WK. Is bone marrow examination in small-cell lung cancer really necessary?. *Ann Intern Med* 1986; 105: 508-12.
- Tritx DB, Doll DC, Ringenberg S, et al. Bone marrow involvement in small cell lung cancer. Clinical significance and correlation with routine laboratory variables. *Cancer* 1989; 63: 763-6.
- Bezwoode WR, Lewis D, Livini N. Bone marrow involvement in anaplastic small cell lung cancer. *Cancer* 1986; 58: 1762-5.
- Doll DC. Serum lactate and bone marrow involvement in small-cell carcinoma of the lung. *N Engl J Med* 1985; 312: 1262.
- Hamrick RM, Murgo AJ. Lactate dehydrogenase values and bone scans as predictors of bone marrow involvement in small-cell lung cancer. *Arch Intern Med* 1987; 147: 1070-1.
- Johnson DH, De Leo M, Greco FA. Bone marrow examination in small cell lung cancer (Letter). *Ann Intern Med* 1987; 106: 170-1.
- Jamshidi K, Swain W. Bone marrow biopsy with unaltered architecture. A new biopsy device. *J Lab Clin Med* 1971; 77: 335-42.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Am Stat Assoc* 1958; 53: 457-81.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. *Br J Cancer* 1977; 35: 1-39.
- Hansen HH, Dombrowsky P, Hirsch FR. Staging procedures and prognostic features in small cell anaplastic bronchogenic carcinoma. *Semin Oncol* 1978; 87: 59-62.
- Hirsch FR, Hansen HH, Hainan B. Bilateral bone marrow examinations in small-cell anaplastic carcinoma of the lung. *Acta Pathol Microbiol Scand (A)* 1979; 87: 59-62.
- Lawrence JB, Eleff M, Behm FG, Johnston CL. Bone marrow examination in small cell carcinoma of the lung. Comparison of trephine biopsy with aspiration. *Cancer* 1984; 53: 2188-90.
- Meinhausen J, Choritz H, Georgii A. Frequency of skeletal metastases as revealed by routinely taken bone marrow biopsies. *Virchow Arch [A]* 1980; 389: 409-17.
- Kelly BW, Morris JF, Harwood BP, Bruya TE. Methods and prognostic value of bone marrow examination in small cell carcinoma of the lung. *Cancer* 1984; 53: 99-102.
- Idhe DC, Simms EB, Matthews MJ, Cohen MH, Bunn PA, Minna JD. Bone marrow metastases in small cell carcinoma of the lung: Frequency, description and influence on chemotherapeutic toxicity and prognosis. *Blood* 1979; 53: 677-86.
- Mead GM, Williams CJ, Thompson J, Smith AG, Whitehouse JM. Bone marrow examinations in small cell carcinoma of the bronchus: an unnecessary procedure?. *Hematol Oncol* 1985; 3: 159-63.
- Levitan N, Byrne RE, Bromer RE, et al. The value of the bone scan and bone marrow biopsy in staging small cell lung cancer. *Cancer* 1985; 56: 652-4.
- Idhe DC, Makuch RW, Carney DN, et al. Prognostic implications of the stage of disease and sites of metastases in patients with small cell carcinoma of the lung treated with intensive combination chemotherapy. *Am Rev Respir Dis* 1981; 123: 500-7.

22. Muss HB, Jackson DV Jr, Richards F, et al. Bone marrow evaluation in small cell lung cancer. *Am J Clin Oncol* 1984; 7: 59-63.
23. Østerlind K, Hirsch FR, Pedersen AG. Serum lactate deshydrogenase and bone marrow metastases in small-cell carcinoma of the lung. *N Engl J Med* 1985; 313: 759.
24. Johnson DH, Greco FA. Serum lactate dehydrogenase and bone marrow metastases in small-cell carcinoma of the lung. *N Engl J Med* 1985; 313: 759-60.
25. Hirsch FR, Hansen HH. Bone marrow involvement in small cell anaplastic carcinoma of the lung. Prognostic and therapeutic aspects. *Cancer* 1980; 46: 206-11.