Bone Marrow Metastases in Small Cell Carcinoma of the Lung: Frequency, Description, and Influence on Chemotherapeutic Toxicity and Prognosis

By Daniel C. Ihde, Elisabeth B. Simms, Mary J. Matthews, Martin H. Cohen, Paul A. Bunn, and John D. Minna

The frequency, pathologic features, and clinical implications of bone marrow metastases were reviewed in 73 previously untreated patients with small cell carcinoma of the lung given intensive combination chemotherapy. After unilateral posterior iliac crest marrow examination and other staging procedures, 26 patients (36%) proved to have limited disease (confined to one hemithorax and regional lymph nodes); the 47 patients with more extensive tumor included 14 (19%) with marrow involvement and 33 (45%) without it. Patients with marrow metastases had tumor documented in more extrathoracic sites than did other patients with extensive disease; the marrow was the sole site of metastatic tumor in only one instance. No patient with a negative marrow biopsy had cancer detected in touch preparation or aspirate. Marked bone remodeling and myelofibrosis were associated with tumor infiltration in 9 of 14 cases. During intensive induction chemotherapy, patients with positive bone marrows had more severe infections and required more red blood cell transfusions (both trends of borderline significance), but leukopenia, thrombocytopenia, and the need for platelet transfusions did not differ in the three groups. Limited disease patients had significantly superior complete response rates to treatment and longer survival than those with extensive disease, but the results of therapy in patients with marrow involvement were not significantly worse than in other patients with extrathoracic metastatic tumor.

In small cell carcinoma of the lung, as in most malignant neoplastic diseases, the extent of tumor dissemination at the time of diagnosis is an important predictor of survival. Bone marrow metastases are found at autopsy in 35%-55% of patients with small cell cancer. Marrow tissue is easily accessible for histologic examination, and it has been sampled prior to therapy by most physicians treating this tumor since early reports indicated a high frequency of involvement at the time of diagnosis. However, the prognostic implications of initial bone marrow metastases in small cell carcinoma have yet to be clearly defined.

For several years small cell lung cancer patients on our unit have been treated with intensive combination chemotherapy after a thorough staging evaluation; during therapy many of these staging procedures are repeated. This policy has provided an opportunity to review our data on bone marrow involvement by small cell carcinoma. In this analysis we have attempted to determine (1) the frequency and clinical correlates of initial marrow metastases, (2) their pathologic features,
(3) the effect of marrow involvement on the toxicity of intensive treatment, and (4) its effect on response to therapy and survival.

MATERIALS AND METHODS

From July, 1975, through June, 1977, 77 consecutive previously untreated patients with histologically confirmed diagnoses of small cell carcinoma of the lung were given intensive combination chemotherapy on our unit. The pathologic material from the pretreatment bone marrow examinations was available for review for 73 patients, and they are the subjects of this report.

Unilateral posterior iliac crest bone marrow examination, including aspiration, biopsy with a Jamshidi or Westerman-Jensen needle, and a touch preparation of the biopsy, was performed in all patients. Biopsies were stained with hematoxylin and eosin (H&E), Giemsa, and/or periodic acid Schiff reagents. Touch preparations of the specimens were made immediately after the biopsy and were stained with Wright-Giemsa and H&E. Other pretreatment staging procedures included history and physical examination, chest roentgenogram, fiberoptic bronchoscopy, bone, brain, and liver scans, and, in some cases, percutaneous liver biopsy. Radiographic bone surveys were not routinely done. Thereafter, patients with tumor limited to one hemithorax, the mediastinum, and ipsilateral supraclavicular lymph nodes were designated as having limited disease (called L in this report). The patients with more extensive tumors were divided into those with bone marrow involvement (the M group) and those without it (the E group). The initial diagnostic pathologic material was reviewed, and tumors were classified as lymphocyte-like (oat cell) or intermediate-type small cell carcinoma or a mixture of the two. Bone marrow examination was repeated after 6 and 24 wk of therapy in most patients and at other times when a new complete response or progression of tumor was suspected; 152 follow-up marrow examinations were done in 55 patients (mean 2.8 per patient). The initial laboratory findings, the various factors reflecting the toxicity of the first 6 wk of chemotherapy, the response of tumor to treatment, and the survival were abstracted from the patients' clinical records. Patients in the M group who had subsequent marrow examinations without detection of malignant cells were called responders in the bone marrow. For a patient to be designated as a complete responder, the disappearance of clinical and pathologic evidence of tumor in all known sites was required; a partial response was defined as a reduction of 50% or more in the sum of all measurable and evaluable tumor masses. Survival was measured from day 1 of chemotherapy to death or until February, 1978, with a range of observation times of 8–29 mo in living patients.

All 73 patients received 6 wk of intensive induction chemotherapy with cyclophosphamide, methotrexate, and CCNU, without dosage modification for hematologic toxicity. The first 64 were given cyclic alternating combination chemotherapy until relapse. Nine later patients received the same drugs, with an increased dosage of cyclophosphamide during induction; this group was also given chest irradiation after 12 wk on chemotherapy. The statistical significance of the differences in quantitative data among M, E, and L patients was assessed with a one-tailed Kruskal-Wallis test; differences between two groups were analyzed with a one-tailed two-sample rank test. The chi-square test was used to analyze differences in enumeration data. Differences in survival between groups were compared with a log rank test, and survival was plotted by the life table method.

RESULTS

Detection and Correlates of Marrow Metastases at Diagnosis

Tumor in bone marrow (M) was found in 14 patients (19%); 33 patients (45%) had extensive disease without marrow involvement (E), and 26 patients (36%) had limited disease (L). The frequency of marrow involvement was not affected by the histologic subtype of small cell carcinoma (23% with lymphocyte-like, 15% with intermediate type, and 18% with mixed, p > 0.30), but involvement was more common in patients with extensive disease. Of those patients in whom any staging procedure other than bone marrow examination documented extensive disease, 13 of 46 patients (28%) were in the M group, whereas only 1 of 27 patients (4%) with
Table 1. Hematologic Findings Prior to Therapy in 73 Patients With Small Cell Carcinoma of the Lung

<table>
<thead>
<tr>
<th></th>
<th>Extensive Disease</th>
<th>Limited Disease</th>
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<tbody>
<tr>
<td></td>
<td>Marrow Positive</td>
<td>Marrow Negative</td>
</tr>
<tr>
<td></td>
<td>(14 Patients)</td>
<td>(33 Patients)</td>
</tr>
<tr>
<td><strong>WBC count (cells/µl)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9,200</td>
<td>8,700</td>
</tr>
<tr>
<td>Range</td>
<td>1,500–14,600</td>
<td>5,500–14,100</td>
</tr>
<tr>
<td><strong>Hematocrit (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>36.4</td>
<td>37.0</td>
</tr>
<tr>
<td>Range</td>
<td>28–44</td>
<td>29–44</td>
</tr>
<tr>
<td><strong>Platelet count (x 10^3/µl)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>316</td>
<td>387</td>
</tr>
<tr>
<td>Range</td>
<td>76–583</td>
<td>150–586</td>
</tr>
<tr>
<td><strong>Reticulocyte count (%)</strong>†</td>
<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Range</td>
<td>0.2–5.9</td>
<td>0.2–6.2</td>
</tr>
<tr>
<td><strong>Leukoerythroblastic smear</strong></td>
<td>5/14</td>
<td>1/33</td>
</tr>
<tr>
<td>(no. patients/no. examined)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe anemia or other cytopenia (no. patients)</strong>§</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Borderline lower in marrow-positive patients (p < 0.10).
†Data on 51 patients.
‡Significantly more frequent in marrow-positive patients (p < 0.001); 2% or more nucleated RBCs + immature WBCs (metamyelocyte or younger) on differential count.
§Hct < 30, WBC < 4000, or platelets < 150,000.

negative results in all other staging procedures had marrow involvement diagnosed. M patients had extensive disease in a mean of 3.1 sites; E patients, in 1.6 sites. Among the M group, 12 patients (86%) had positive bone scans and 11 patients (79%) had liver metastases. Only liver involvement was significantly correlated (p < 0.05) with marrow metastases among extensive disease patients; the 73% frequency of positive bone scans in E patients was quite similar to the 86% rate of abnormal bone scintigrams in the M group. Hematologic findings prior to therapy are given in Table 1. Platelet counts were modestly lower (M versus E versus L, p < 0.10; M versus E and L, p < 0.05; borderline significance) in M cases, and leukoerythroblastic peripheral smears were found almost exclusively in this group (p < 0.001). Cytopenias other than mild anemia were infrequent in our patients, but 2 of the 4 patients with such cytopenias were in the M group.

Red blood cell (RBC) indices and serum folate and vitamin B12 levels determined before therapy did not vary significantly among the M, E, and L groups. However, alkaline phosphatase values were significantly (M versus E versus L, p < 0.01) elevated in M patients.

Pathologic Findings

Bone marrow biopsies revealed invasion by cancer in all 14 M patients. In nine of the biopsies (64%) there were marked osteoblastic and myelofibrotic processes associated with the metastases, mimicking those associated with prostatic and breast malignancies. The lamellar patterns of trabeculae were disorganized and showed evidence of recent or remote osteoclastic bony resorption. Trabeculae were
thickened because of broad osteoid bands applied to the preexisting eroded trabeculae, giving the bone a remodeled pagetoid appearance. Marrow spaces were encroached on and partially replaced by osteoid spicules lined by osteoblasts (Fig. 1). This marked osteoblastic reaction was noted in all 7 patients with serum alkaline phosphatase values above the median for M patients.

In zones of tumor metastases the marrow was also infiltrated or replaced by loose fibrous tissue containing dilated lymphatic channels. Neoplastic cells were arranged in anastomosing sheets or nests; they had enlarged vesicular nuclei, indistinct nucleoli, and moderate amounts of cytoplasm. These striking changes of new bone formation and fibrosis were not observed in biopsies from any E or L patients. In none of the M patients' biopsies was there extensive destruction or replacement of the bony structure by tumor. In 5 patients marrow involvement was focal and was associated with minimal bony or hematopoietic changes. The histologic subtypes of small cell cancer seen in marrow biopsies did not correlate with the subtypes observed in the diagnostic pathologic material from the same patients.

Touch preparations were available in 13 patients with positive marrow biopsies, and 12 were positive for cancer. Neoplastic cells clustered in groups of 6–12; they had scanty but distinct cytoplasm and showed nuclear molding and indistinct nuclear characteristics. This technique provided a rapid method of diagnosis, particularly when aspirates were unobtainable because of dry taps. The identification of numerous osteoblasts and osteoclasts, especially in Wright-Giemsa stains, accurately reflected the unusual bone remodeling seen in the corresponding biopsies.
Fig. 2. Appearance of small cell carcinoma cells in bone marrow aspirate (Wright-Giemsa stain, ×1700). Tumor cells occur in clusters; they have molded nuclei and are two to three times the size of a mature lymphocyte.

Dry taps were recorded in 8 M patients (56%) with marked osteosclerotic reaction. Marrow aspiration was unsuccessful in only 3 of 59 E and L patients. Five of the six aspirates obtained from M patients were positive. Neoplastic cells were similar (Fig. 2) to those described in the touch preparations.

Toxicity of Induction Chemotherapy

Of the total dose of cyclophosphamide planned for the 6-wk induction period, a mean of 105% was given to M, 100% to E, and 107% to L patients. The hematologic, infectious, and fatal toxicities of intensive induction chemotherapy in our patients and the hematologic support required during this period are summarized in Table 2. The numbers of days of moderate and severe leukopenia and thrombocytopenia and the numbers of platelet transfusions required were no different among the M, E, and L patients. Patients with marrow involvement required more RBC transfusions (M versus E versus L, \( p < 0.10 \); M versus E and L, \( p < 0.05 \); borderline significance) and had more (\( p < 0.10 \), borderline significance) microbiologically documented severe infections (sepsis and/or pneu-
Table 2. Effect of Bone Marrow Metastases on Hematologic and Infectious Toxicity of 6-wk Induction Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Extensive Disease, Marrow Positive (14 Patients)</th>
<th>Extensive Disease, Marrow Negative (33 Patients)</th>
<th>Limited Disease (26 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days moderate leukopenia</td>
<td>18.5 (2–32)†</td>
<td>17.2 (5–31)</td>
<td>18.6 (5–38)</td>
</tr>
<tr>
<td>Days severe leukopenia</td>
<td>10.7 (0–25)†</td>
<td>8.8 (0–28)</td>
<td>10.5 (0–25)</td>
</tr>
<tr>
<td>Days moderate thrombopenia</td>
<td>5.2 (0–24)§</td>
<td>2.8 (0–17)</td>
<td>3.3 (0–18)</td>
</tr>
<tr>
<td>Days severe thrombopenia</td>
<td>1.2 (0–13)§</td>
<td>0.8 (0–12)</td>
<td>1.3 (0–8)</td>
</tr>
<tr>
<td>RBC transfusions given (units)</td>
<td></td>
<td>3.1 (0–10)†</td>
<td>1.6 (0–11)</td>
</tr>
<tr>
<td>Platelet transfusions (no.)</td>
<td></td>
<td>1.1 (0–7)§</td>
<td>0.5 (0–6)</td>
</tr>
<tr>
<td>Severe infections [no. (%)]</td>
<td></td>
<td>4 (29%)§</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Induction deaths [no. (%)]</td>
<td></td>
<td>2 (14%)§</td>
<td>3 (9%)</td>
</tr>
</tbody>
</table>

*WBC < 2500/μl.
†Mean (range).
§Platelets < 50,000/μl.
||Platelets < 20,000/μl.
||Borderline higher in marrow-positive patients (p < 0.10).

monitis), but the numbers of deaths during induction were no different among the three groups of patients (p > 0.10).

Response to Therapy and Survival

Marrow involvement with small cell carcinoma was not detected on one or more occasions during chemotherapy in 10 of 12 M patients (83%) with subsequent marrow examinations. However, excessive bone remodeling and marrow fibrosis did not regress. Among the 10 bone marrow responders, 3 of 9 with further serial bone biopsies later relapsed in the marrow. Among all follow-up marrow examinations in M patients, 11 of 31 (35%) were positive for cancer. Marrow involvement during therapy was documented significantly more often in this group than in E (4 of 68 = 6%) or L (2 of 53 = 4%) patients (p < 0.001).

If all sites of tumor involvement are considered, the complete plus partial response rates varied from 85% to 96% among the three groups of patients and were not significantly different (p > 0.15). However, the complete response rate of 62% in L patients was significantly superior to the complete response rate of 36% in all extensive disease patients (p < 0.05). The complete response rates of 29% in M patients and 39% in E patients were not significantly different (p > 0.10).

Fifty-three patients had died by February, 1978, and 20 remained alive. The actuarial median survival of all patients was 11 mo, and survival of the three groups of patients is shown in Fig. 3. Actuarial median survivals were 14 mo for L, 10 mo for E, and 8 mo for M patients. The longer survival of L patients as compared with all patients with extensive disease was of borderline statistical significance (p < 0.10), but the survivals of M and E patients were not significantly different (p > 0.10). However, of 7 extensive disease patients who lived more than 12 mo in complete response, 6 were from the E group, and only 1 was from the M group.

DISCUSSION

Early studies8,9,15,16 reported a high frequency of bone marrow involvement in small cell lung cancer, ranging from 32% to 46%. Marrow examination was often
found to be positive in patients who would otherwise have been classified as having limited disease. Our results confirm more recent reports of a lower frequency of initial marrow involvement (17%–24%) and a limited yield of bone marrow examinations when all other staging procedures are negative. Current policies of early systemic treatment for patients with less advanced stages of disease and more aggressive use of staging procedures probably explain these changing findings.

In our small cell carcinoma patients with extensive disease, as in Hansen's more advanced cases, positive bone marrow examinations and abnormal bone scans were found to occur independently. Thus, these two procedures may not simply be different means of detecting the same site or volume of disease. We have confirmed the data of Hirsch et al. that marrow positivity occurs with similar frequencies among the histologic subtypes of small cell carcinoma. However, small cell subtypes have often differed in the marrow and diagnostic pathologic material (usually from lung or node) in individual patients. This is consistent with our finding that variability of subtype may be demonstrated in serial sections of the same biopsy or serial biopsies from the same patient. Most of our M patients had normal peripheral blood counts, except for modest degrees of anemia, but leukoerythroblastic peripheral smears were seen in 36%. Hirsch et al. have reported that thrombocytopenia or leukoerythroblastic smears are highly suggestive of marrow involvement by this tumor.

Bone marrow biopsy detected all cases of marrow involvement in our patients; touch preparations and aspirates were never positive when the biopsy was negative. This greater sensitivity of the marrow biopsy agrees with the findings in most studies in solid tumor patients in which biopsy has been compared with other methods for the diagnosis of marrow metastases. Hirsch et al. found aspirates to be more sensitive than biopsies in detecting marrow involvement in small cell
cancer, and they speculated that their results might be due to the limited amounts of fibrous stroma in marrows infiltrated with metastatic tumor. We doubt this explanation because of the frequent finding of myelofibrosis in the positive biopsies in our patients. Bilateral iliac crest biopsies would probably have increased the detection of marrow metastases in our patients. However, the significantly higher frequency of positive marrows during chemotherapy in our M patients than in our E and L patients confirms the validity of a single initial unilateral biopsy in distinguishing these groups.

Osteoblastic and fibrotic reactions in marrows invaded by metastatic cancer are not uncommon, particularly in mammary and prostatic cancer. Milch and Changus studied bone metastases from primary lung cancers in 20 autopsied patients and found that reactive bone production was predominant over bone destruction in 7 patients. We have previously noted these pathologic abnormalities in the marrow of small cell carcinoma patients during therapy and at autopsy. The osteoblastic metastases seen radiographically in small cell cancer are consistent with the osteosclerotic histologic process.

The toxicity of induction chemotherapy was not markedly worse in our M patients than in those without marrow involvement, although there was a suggestion that the M group required more RBC transfusions and had more severe infections. Eagan et al. found that marrow involvement did not affect the hematologic toxicity of therapy in their patients with small cell cancer; Holoye et al. observed more severe hematologic toxicity in their patients with marrow metastases, but their results were not analyzed statistically. The toxicity of combination chemotherapy is reported to be greater in metastatic breast cancer patients with bone marrow involvement. Increased hematologic toxicity to MOPP treatment in Hodgkin’s disease patients with marrow involvement was confined to those patients with initial leukopenia.

We found that metastatic tumor in bone marrow was responsive to combination chemotherapy in 83% of our patients, excluding two cases in which there were early deaths and no subsequent examinations. Despite elimination of tumor from the marrow in many of our patients, the initially noted fibrotic and osteosclerotic changes did not regress; this is in contrast to observations made in marrow-positive Hodgkin’s disease patients who achieved complete remission. Other studies of marrow involvement in small cell cancer have not reported response by site. Bone marrow involvement may not have had an intrinsic deleterious effect in our patients, since it was neither poorly responsive to treatment nor associated with excessive chemotherapeutic toxicity. However, it was an indicator of more disseminated tumor. More sites of extensive disease and a higher frequency of liver metastases were demonstrated in our M patients than in our E patients. Furthermore, the M patients were at greater risk for eventual extension of tumor to the central nervous system.

Although inferior therapeutic results might be expected in a group of patients with apparently greater tumor burdens, the complete response rate and survival in our M patients were not statistically significantly worse than results in our remaining patients with extensive disease. Hansen found identical median survivals in his marrow-positive and marrow-negative groups, and Holoye et al., using a more intensive therapeutic regimen, also observed similar complete response rates and survival in patients with extensive small cell carcinoma without regard to
Marrow involvement. The lack of effect of metastatic marrow infiltration on response and survival in patients treated for disseminated tumor has also been reported in breast carcinoma\textsuperscript{25} and stage IV Hodgkin’s disease.\textsuperscript{26} Hence, the currently available data appear to support the present policy\textsuperscript{3,4,25} of giving equally aggressive treatment to patients with extrathoracic small cell lung cancer whether or not bone marrow metastases are present.

ACKNOWLEDGMENT

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