Bone Marrow Involvement in Hodgkin’s Disease: Pathology and Response to MOPP Chemotherapy

By C. E. Myers, B. A. Chabner, V. T. De Vita, and H. R. Gralnick

Examination of the bone marrow biopsies of 174 patients with Hodgkin’s disease seen at the National Cancer Institute between 1965 and 1972 revealed tumor involvement of the marrow in 19 cases. Eighteen of the 19 patients were treated with intensive combination chemotherapy (MOPP), and 13 achieved complete remission; the median duration of remission was 25+ mo, and 49% of those at risk remained in continuous remission for at least 3 yr. In all patients with marrow involvement, marrow fibrosis due to increased collagen or reticulin was identified in the pretreatment specimen. Repeat biopsies following therapy revealed entirely normal marrow free of tumor and reticulin or collagen fibrosis in eight patients, although residual collagen was detected in three other patients. Pretreatment leukopenia (WBC less than 5000 cells per cu mm) was present in seven of the 18 patients treated with MOPP, and appeared to be associated with an increased risk of infection and a less favorable response to therapy. These results indicate that nonleukopenic patients with Hodgkin’s disease and bone marrow involvement can be safely and effectively treated with intensive chemotherapy, and that pathologic changes in the marrow, including diffuse myelofibrosis, are often reversible with such therapy.

During the past decade combination chemotherapy has favorably altered the prognosis for patients with advanced Hodgkin’s disease. The MOPP regimen, introduced at the National Cancer Institute in 1965, has produced complete remissions in approximately 75% of patients with disseminated disease and a 5-yr survival rate of 72%. These results have been confirmed in subsequent clinical trials.

However, considerable uncertainty exists as to whether patients with bone marrow involvement can be effectively treated with intensive chemotherapy. The myelosuppressive effects of alkylating agents and procarbazine have deterred clinicians from employing these agents in patients with compromised bone marrow, and a recent report from Stanford indicated that remissions induced in these patients with chemotherapy are usually of brief duration. An additional problem is posed by the extensive myelofibrosis occasionally found in association with Hodgkin’s involvement of bone marrow. Reversal of this lesion with chemotherapy has recently been reported in a single case of Hodgkin’s disease, but in general, neither the responsiveness of marrow invasion with diffuse fibrosis nor its effect on tolerance to chemotherapy is known.

In order to clarify the importance of bone marrow involvement in the management of patients with Hodgkin’s disease, we have undertaken a study of the clinical presentation, pathologic findings, and response to therapy of 19 patients with marrow invasion admitted to the National Cancer Institute between
January 1965 and December 1972. This study indicates that intensive chemotherapy can reverse the pathologic findings and produce prolonged remissions in the majority of patients with pretreatment bone marrow involvement.

**MATERIALS AND METHODS**

**Patient Population**

We examined the closed bone marrow biopsies done routinely on all previously untreated patients with Hodgkin's disease admitted to the National Cancer Institute between January 1965 and December 1972. Of the 250 patients thus evaluated, 174 of these patients had closed bone marrow biopsies which were sufficiently large and free of artifact to allow evaluation of the marrow cellularity, the marrow morphology, evidence of fibrosis, and/or tumor involvement. In 19 of these patients bone marrow involvement was recognized.

**Bone Marrow Evaluation**

Pretreatment bone marrow biopsies were obtained routinely on all new patients using a modified Vim-Silverman or Westerman-Jensen needle. The specimens obtained were then fixed, decalcified, and sectioned as previously reported. Biopsy sections were stained with hematoxylin and eosin, and in cases where fibrosis was suspected, additional sections were prepared with Masson-Trichrome stain for collagen and the Hortega-Foote stain for reticulin. Clot sections and marrow aspirates were also examined for details of particle histology and cellular morphology.

Biopsies were considered positive when the normal marrow architecture was disrupted with typical Reed-Sternberg cells situated within swirls of fibrous tissue containing lymphocytes, plasma cells, eosinophils, and fibroblasts. In addition, marrows were considered positive if large mononuclear cells with nuclear features of Reed-Sternberg cells were seen within the above-mentioned background and if Reed-Sternberg cells had been previously identified in a lymph node biopsy. These criteria are similar to those reported previously by Webb et al. and are consistent with the guidelines established at the Ann Arbor Symposium on Staging in Hodgkin's Disease. Serial sections were cut and examined in all biopsies considered suspicious of bone marrow involvement in which classical Reed-Sternberg cells were not identified. Reticulin fibrosis was defined as the presence of increased reticulin fibers without superimposed collagen, while biopsies containing increased collagen with or without reticulin were categorized as positive for collagen fibrosis (myelofibrosis).

A basic question posed by the present study was whether patients with positive marrow can be treated as effectively with MOPP as patients with other sites of stage IV disease. Accordingly, the results of therapy in patients with positive marrow were compared to those in 30 patients having other sites of extranodal disease. These 30 patients included all stage IV patients with negative marrow treated with MOPP between January 1964 and July 1967, and were described in a previous report. The actuarial survival curves of patients with and without marrow involvement were calculated using the method Berkson and Gage.

**Patient Treatment**

Patients with marrow involvement were treated with MOPP chemotherapy in accordance with the previously published protocol from this institution. Dosage modification was determined by the peripheral white count and platelet count according to this protocol, except that patients received full doses of all drugs for the initial course of treatment irrespective of peripheral blood counts. Upon completion of six cycles of therapy, remission induction was verified by a thorough clinical evaluation, including repeat biopsy of previously involved organs.

**RESULTS**

**Pretreatment Marrow Involvement**

Fifteen of 174 patients with adequate marrow biopsies had marrow involvement as indicated by Reed-Sternberg cells in 11 biopsies. In four cases with
well-established Hodgkin’s disease, multiple closed biopsies revealed malignant histocytes but no Reed-Sternberg cells within a fibrotic tissue containing lymphocytes, plasma cells, eosinophils, and fibroblasts. Four other patients exhibited diffuse myelofibrosis in multiple biopsies, but lacked identifiable malignant cells; these biopsies were considered positive in the light of subsequent identification of malignant cells within the fibrotic marrow at autopsy, and in the absence of another explanation for myelofibrosis.

In six patients the involvement was focal, consisting of discrete areas of malignant and inflammatory cells and fibrosis in otherwise normal specimens. In 13 patients, the marrow biopsy was diffusely replaced by fibrosis, with little residual hemopoiesis. In each biopsy, reticulin or collagen was identified by special histologic stains. Collagen was identified in 12 of the positive biopsies, including 11 of the 13 with diffuse marrow involvement, and in one of the six biopsies with focal abnormalities. The remaining biopsies contained reticulin fibrosis.

Clinical Features of Patients With Positive Bone Marrow

The clinical features of patients with bone marrow involvement were compared with those of 30 patients having negative marrow biopsies.

Several significant differences were evident, as shown in Tables 1 and 2; the sex distribution was heavily weighted toward males, and there were significantly fewer cases of nodular sclerosis type pathology in patients with marrow involvement. B symptoms were common in both groups, occurring in 27 of 30 with negative marrow biopsies and 18 of 19 with positive marrow.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Other Extramedullary Sites</th>
<th>Nodal Pathology</th>
<th>Pattern of Marrow Involvement</th>
<th>Therapy</th>
<th>Duration of Remission (mo)</th>
</tr>
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<tbody>
<tr>
<td>R.C.</td>
<td>21</td>
<td>M</td>
<td>—</td>
<td>L.D.</td>
<td>Focal</td>
<td>MOPP</td>
<td>N.R.†</td>
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<tr>
<td>M.F.</td>
<td>32</td>
<td>M</td>
<td>Liver</td>
<td>M.C.</td>
<td>Focal</td>
<td>MOPP</td>
<td>N.R.</td>
</tr>
<tr>
<td>R.G.</td>
<td>34</td>
<td>M</td>
<td>—</td>
<td>Unc.</td>
<td>Focal</td>
<td>MOPP</td>
<td>30 +</td>
</tr>
<tr>
<td>E.H.</td>
<td>52</td>
<td>M</td>
<td>Liver</td>
<td>Unc.</td>
<td>Focal</td>
<td>VELBAN</td>
<td>N.R.</td>
</tr>
<tr>
<td>J.P.</td>
<td>50</td>
<td>M</td>
<td>—</td>
<td>M.C.</td>
<td>Focal</td>
<td>MOPP</td>
<td>50 +</td>
</tr>
<tr>
<td>M.S.</td>
<td>48</td>
<td>F</td>
<td>Bone</td>
<td>L.D.</td>
<td>Focal</td>
<td>MOPP</td>
<td>16 +</td>
</tr>
<tr>
<td>T.A.</td>
<td>18</td>
<td>M</td>
<td>Bone</td>
<td>N.S.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>10</td>
</tr>
<tr>
<td>G.B.</td>
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<td>M</td>
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<td>N.S.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>8</td>
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<tr>
<td>I.B.</td>
<td>49</td>
<td>M</td>
<td>Skin, Lung</td>
<td>L.D.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>N.R.</td>
</tr>
<tr>
<td>J.C.</td>
<td>47</td>
<td>M</td>
<td>Liver, Ascites</td>
<td>M.C.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>25 +</td>
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<tr>
<td>W.Gr.</td>
<td>32</td>
<td>M</td>
<td>—</td>
<td>L.D.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>56 +</td>
</tr>
<tr>
<td>W.N.</td>
<td>37</td>
<td>M</td>
<td>—</td>
<td>L.D.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>53 +</td>
</tr>
<tr>
<td>J.Ra.</td>
<td>45</td>
<td>M</td>
<td>Skin</td>
<td>L.D.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>76 +</td>
</tr>
<tr>
<td>J.Ro.</td>
<td>43</td>
<td>F</td>
<td>—</td>
<td>M.C.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>25 +</td>
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<tr>
<td>A.S.</td>
<td>29</td>
<td>M</td>
<td>Bone</td>
<td>L.D.</td>
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<td>MOPP</td>
<td>76 +</td>
</tr>
<tr>
<td>E.S.</td>
<td>22</td>
<td>M</td>
<td>Bone</td>
<td>Unc.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>N.R.</td>
</tr>
<tr>
<td>N.S.</td>
<td>19</td>
<td>F</td>
<td>Lung, Bone</td>
<td>N.S.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>12 +</td>
</tr>
<tr>
<td>P.T.</td>
<td>59</td>
<td>M</td>
<td>Liver</td>
<td>L.D.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>7</td>
</tr>
<tr>
<td>D.Z.</td>
<td>37</td>
<td>M</td>
<td>Bone, Liver</td>
<td>M.C.</td>
<td>Diffuse</td>
<td>MOPP</td>
<td>N.R.</td>
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</tbody>
</table>

*N.S., nodular sclerosis; M.C., mixed cellularity; L.D., lymphocyte depletion; Unc., unclassified.
†N.R., No remission; +, still in remission.
Table 2. Pretreatment Clinical Characteristics of Patients With and Without Marrow Involvement

<table>
<thead>
<tr>
<th></th>
<th>Nodal Pathology</th>
<th>Mean Blood Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex M/F</td>
<td>Age</td>
</tr>
<tr>
<td>Morrow Positive</td>
<td>15/4</td>
<td>38</td>
</tr>
<tr>
<td>Morrow Negative</td>
<td>14/16</td>
<td>31</td>
</tr>
</tbody>
</table>

*P < 0.025 N. Sig. N. Sig. < 0.05 N. Sig. N. Sig. < 0.01 N. Sig. N. Sig.

*L.P., lymphocyte predominant; N.S., nodular sclerosis; M.C., mixed cellularity; L.D., lymphocyte depletion; Unc., unclassified.

†Cells x 10³/mm

‡By Fisher's exact test or Student's t test; N. Sig., not significant.

The pretreatment blood counts were of interest as a possible factor in determining tolerance to chemotherapy (Table 2). Patients with pretreatment marrow involvement had a median white count within the normal range, which contrasts with the frequent leukocytosis and mean white count of 12 x 10³ cells per cu mm seen in those patients with negative marrow biopsies. Seven of the 19 patients with positive marrow were leukopenic (white count less than 5000 cells per cu mm) prior to therapy. There was little correlation between peripheral white count and the extent of marrow involvement on biopsy, as only two of 13 patients with diffuse marrow invasion on biopsy were leukopenic, as opposed to five of six patients with focal involvement. The median platelet counts were similar for the two groups; only two of 19 patients with positive marrow and none of the 30 with negative marrow biopsies exhibiting thrombocytopenia (platelet count less than 150,000 cells per cu mm). Thrombocytosis (platelet counts greater than 400,000) was commonly seen in both groups, occurring in seven patients with positive marrow and 12 without marrow involvement.

Anemia, a common finding in patients with stage IV disease irrespective of bone marrow involvement, occurred with equal frequency in patients with and without marrow involvement. Further, the degree of anemia did not appear related to the extent of marrow replacement.

Response to Therapy

Eighteen of 19 patients with positive marrow were treated with MOPP chemotherapy, while one patient (E. H.) was treated with Velban. Of the 18 patients receiving MOPP, 13 entered complete remission. Three have since relapsed at 7, 8, and 10 mo after completion of therapy, while ten patients remain in remission after a median follow-up period of 30 mo with a range of 12–76 mo. There was no apparent relationship between the extent of marrow involvement as judged by marrow biopsy and the response to chemotherapy, as ten of 13 patients with diffuse involvement entered complete remission, while three of five with focal involvement achieved this status. The actuarial survival curves for patients with and without marrow involvement are shown in Fig. 1, and indicate no difference in survival for the two groups, the median survival for the group with positive marrow being at least 25 mo. The disease-free
survival curves in Fig. 2 indicate that the duration of complete remission in the two groups will be comparable. There have been no relapses past 18 mo in patients with pretreatment marrow involvement.

Intensive combination therapy proved to be least successful in patients with bone marrow invasion and white counts less than 5,000 cells per cu mm prior to therapy (Table 3). Only three of seven patients achieved a complete remission, as compared to ten of 11 patients with white counts greater than 5000. The lower frequency of remission was reflected in a median survival of only 9 mo in this group of leukopenic patients. Two patients in this group, however, remain free of disease 16 and 30 mo after therapy.
Table 3. Effect of Pretreatment W.B.C. on Response to Therapy

<table>
<thead>
<tr>
<th>Pretreatment W.B.C.</th>
<th>Positive Marrow (18 patients)</th>
<th>Negative Marrow (30 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5,000 (11 pts)</td>
<td>3300</td>
<td>2300</td>
</tr>
<tr>
<td>&lt;5,000 (7 pts)</td>
<td>2300</td>
<td>4200</td>
</tr>
<tr>
<td>Life-threatening infections Per cent protocol therapy*</td>
<td>80-90</td>
<td>80-90</td>
</tr>
<tr>
<td>Complete remissions</td>
<td>10/11</td>
<td>3/7</td>
</tr>
<tr>
<td>Median survival (mo)</td>
<td>&gt;25</td>
<td>9</td>
</tr>
</tbody>
</table>

*Median

Tolerance to Intensive Chemotherapy

A major question to be answered by this study was whether patients with marrow involvement would experience a high incidence of serious complications secondary to myelosuppression during intensive chemotherapy.

The eighteen patients with positive marrow received a median of 80%-90% of protocol therapy, the same as received by the 30 patients with normal marrow (Table 3). However, in the seven patients with positive marrow who were leukopenic prior to treatment, this therapy was given at the expense of a significantly lower mean nadir of the white count and a higher incidence of serious infectious complications. The 11 nonleukopenic patients with positive marrow had a slightly lower mean nadir of the white count than the patients with normal marrow, but experienced only one serious infectious complication during therapy.

Posttherapy Hematologic Status

Eight patients with diffuse fibrosis and three patients with focal Hodgkin’s involvement treated with MOPP have had repeat bone marrow biopsies after therapy to evaluate remission status. In two additional patients, the posttherapy marrow biopsies were judged inadequate for the purposes of this study. Malignant cells or reticulin fibrosis were not seen in any of these 11 post-treatment biopsies. In contrast, collagen fibrosis, which had been present in six of these patients before treatment, was detected in three patients after therapy; in two patients the residual collagen deposits were focal and associated with normal myelopoiesis, but in one patient with documented hepatic extramedullary hematopoiesis, the collagen fibrosis was diffuse. It thus appears that reticulin fibrosis in bone marrow is likely to resolve completely in patients attaining remission, but collagen fibrosis may be irreversible in some cases despite achievement of remission.

Peripheral blood counts returned to normal in ten of 13 patients attaining complete remission. Of the three patients with persistent depression of their white count and hematocrit following therapy, two had residual focal collagen fibrosis on posttreatment marrow biopsy, but no evidence of tumor.

DISCUSSION

The present report has examined the clinicopathologic findings and response to therapy of a series of patients with Hodgkin’s disease involving bone mar-
row. In general, patients with positive marrow exhibited an excellent tolerance and response to intensive combination chemotherapy, as 13 of 18 (72%) so treated achieved complete remission. The duration of complete remission and survival in this group of patients appears comparable to that of stage IV patients lacking bone marrow involvement who received the same therapy. Only in patients with positive marrow who were leukopenic prior to treatment was there evidence of decreased tolerance to myelosuppressive agents, a higher incidence of infectious complications, and a less favorable therapeutic response.

The results of this study contrast with the outcome of combination chemotherapy in a similar series of patients with marrow involvement recently reported by Rosenberg. In the Stanford series, only 21% of patients remained in complete remission at 18 mos, as opposed to 49% at 3 yr in the present series. This difference may be due in part to the differences in pathologic types of Hodgkin's disease seen at the two institutions. Forty-seven per cent of the Stanford patients had nodular sclerosis type of Hodgkin's disease, while only three of 19 patients in the NIH series were found to have this histology. In our experience, relapses following chemotherapy are more frequent among patients with this histologic subtype of Hodgkin's disease. Neiman, Rosen, and Lukes have recently described a group of patients with lymphocyte depletion Hodgkin's disease characterized by fever, pancytopenia, marrow hypoplasia, and a rapidly fatal outcome. However, only three patients received combination chemotherapy. In our series, eight patients with lymphocyte depletion histology and marrow involvement were treated with MOPP (Table 1). Six entered complete remission and only one has relapsed (at 7 mo) while five remain in remission after a follow-up of 16-76 mo. Thus, lymphocyte depletion Hodgkin's disease associated with marrow involvement does not preclude successful treatment with MOPP chemotherapy. Pretreatment leucopenia, regardless of the nodal histology, did have a grave prognostic impact with a median survival after therapy of only 9 mo.

A second finding of importance in this study was the invariable presence of reticulin or collagen fibrosis associated with tumor involvement of marrow, and the reversal of fibrosis in patients responding to chemotherapy. Previous reports have called attention to a fibrotic replacement of bone marrow in occasional patients with Hodgkin's disease, and a similar fibrotic response has been reported in association with other malignancies metastatic to bone marrow, including carcinoma of the stomach, breast, and prostrate. At least one example has been reported of reversal of marrow fibrosis in a patient with Hodgkin's disease treated with MOPP; however, in this case no mention was made of the use of special stains to demonstrate the presence, and later disappearance of reticulin or collagen.

Although the random nature of bone marrow involvement in Hodgkin's disease makes definitive evaluation of bone marrow pathology difficult on the basis of a single needle biopsy, a comparison of pre- and posttreatment biopsies suggests that reticulin fibrosis is readily reversible with chemotherapy. Collagen fibrosis also appeared to reverse with chemotherapy in three patients achieving complete remission, but in three additional cases, either focal or diffuse collagen persisted in posttreatment specimens. From the foregoing results, there appears to be little reason for withholding intensive therapy in nonleukopenic patients.
with bone marrow involvement. Only in those patients with marrow involvement and pretreatment leukopenia did there appear to be an increased risk of infection and a less favorable response to therapy. The ultimate improvement in peripheral blood counts to normal levels in patients achieving complete remission was a strong indication of the beneficial effects of tumor irradiation in restoring normal hematopoiesis, which more than compensated for the deleterious effects of chemotherapy on marrow function.

REFERENCES

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