The Treatment of Malignant Histiocytosis

By Alexander Tseng, Jr, C. Norman Coleman, Richard S. Cox, Thomas V. Colby, Roderick R. Turner, Sandra J. Horning, and Saul A. Rosenberg

MALIGNANT HISTIOCYTOSIS (MH) is an aggressive and usually rapidly fatal malignancy that is pathologically characterized by a neoplastic proliferation of histiocytes, predominantly within lymphoid and hematopoietic organs. The term “malignant histiocytosis” was introduced in 1966 by Rappaport, although this disease was originally described in 1939 by Scott and Robb-Smith under the name of histiocytic medullary reticulosis.2 Wannke and Kim,3 as well as Byrne and Rappaport,1 have defined morphological criteria for the diagnosis of MH in lymph-node biopsies. More recent studies using immunologic, cytochemical, and ultrastructural techniques support the concept that the malignant cells in most cases belong to the mononuclear-phagocyte system.4,5 However, MH must be histologically distinguished from benign histiocytic-macrophagic proliferations, such as viral-associated hemophagocytic syndrome,6 and from the malignant disorders, ie, erythrophagocytic T-gamma lymphoma,7 and diffuse large-cell lymphomas of “true histiocytic” origin.8 Distinction of MH from the latter two may be difficult, and sometimes arbitrary, on morphological grounds alone.

The classic clinical manifestations of MH include fever, sweats, weakness, malaise, hepatomegaly, splenomegaly, and lymphadenopathy. However, it is not unusual for patients to present with other organ system involvement, including sites such as lung, CNS, pericardium, bone, skin, soft tissue, and intestinal tract.9-12 Without treatment, the disease is universally fatal, with death often occurring within weeks to months. Early studies in small numbers of patients reported disappointing results using single-agent chemotherapy or combination chemotherapy regimens, such as CVP (cyclophosphamide, vincristine, and prednisone).3 Alexander and Daniels found that the median duration of survival for responders to CVP was approximately 9 months from the onset of symptoms.13 The incorporation of Adriamycin in a variety of treatment regimens has been reported to be more successful. The total number of patients treated, however, remains small, and long-term follow-up data have not been reported.14,15 Therefore, we have retrospectively reviewed our experience with patients diagnosed as having MH who were aggressively treated with combination chemotherapy that included Adriamycin as one of the agents.

MATERIALS AND METHODS

All cases of malignant histiocytosis were evaluated and treated by the Division of Oncology, Stanford University Medical Center, between 1973 and 1983. Seven of these cases have been previously reported.17 The histologic sections from patients were reviewed by one of us (T.V.C.). The diagnosis of malignant histiocytosis was
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based on the criteria used by Warnke et al. The following histologic features were assessed on a scale from 0 to 3: plasma cells, eosinophils, germinal centers, sclerosis, necrosis, atypical small lymphocytes, and large hyperlobated malignant cells. The presence of erythrophagocytosis was also noted.

In six patients, pathologic tissue was further characterized by frozen section immune histochemistry. Surgical specimens were sent to the Stanford Laboratory of Tissue Immunodiagnosis. A more comprehensive immunologic and enzymatic characterization of these cases is included in another study. Clinical evaluation in all patients included physical examination, complete blood count (CBC), blood chemistry panel, and PA and lateral chest roentgenogram. In the initial work-up of patients, there were 22 bone marrow biopsy specimens, six bone marrow aspirates, and 17 lumbar punctures. Less common procedures included a liver biopsy specimen in 11 patients, splenectomy in seven patients, and lung biopsy in three patients. Patients were staged according to the Ann Arbor criteria for Hodgkin's disease.

At the completion of staging, patients were treated with combination chemotherapy regimens containing Adriamycin. The basic regimen was CHOP chemotherapy (cyclophosphamide, Adriamycin, vincristine, prednisone). This was modified in a number of patients to include bleomycin (B) and/or high-dose methotrexate (HD-MTX). Patients were retrospectively placed into two treatment groups: group no. 1, CHOP/B-CHOP, used in seven patients; and group no. 2, CHOP/B-CHOP with (HD-MTX) and leucovorin rescue, used in 15 patients (Table 2). The doses and schedule of CHOP chemotherapy have been previously reported. Bleomycin was given at 4 U/m² IV day 1, and HD-MTX was given IV on day 10. The administration of HD-MTX

was variable. Doses ranged from 0.25 g/m² to 20 g/m², with only one patient receiving <1 g/m². The administration varied from a half-hour to a 6-hour infusion. Twenty-four hours after the infusion of HD-MTX, leucovorin was given at a dose of 10 mg/m² every 6 hours for 10 doses. Drug treatment was repeated at 3-week intervals.

Seven patients in group no. 2 received prophylactic intrathecal methotrexate (12 mg), and one patient also received whole-brain radiotherapy (3,000 rad). Involved-field radiation was used in six patients with palliative intent after they developed progressive disease.

The dosage of chemotherapy was reduced in seven patients because of leukopenia and thrombocytopenia. Four of these patients also had an elevated serum bilirubin. Dose reduction of up to 50% for all agents, except vincristine and prednisone, or the use of nonmyelosuppressive drugs (ie, bleomycin, vincristine, prednisone) was done in these patients. The dose of Adriamycin was reduced in three patients because of an elevated serum bilirubin. These patients were not leukopenic or thrombocytopenic. Reductions of 33%-50% were done for at least two cycles of chemotherapy before 100% doses of Adriamycin could be instituted.

Complete response (CR) was defined as a total regression of all demonstrable tumor, with no new site of malignancy developing. Verification of CR in patients with a previously positive bone marrow required a repeat bone marrow examination. A partial response (PR) was defined as a ≥50% reduction of measurable disease (as measured by the product of perpendicular diameters of measurable disease sites), with no new site of malignancy developing. Duration of response was calculated from the day an objective response was first noted. Duration of survival was calculated from date of diagnosis to the date of death or to the date of the last follow-up visit.

Survival curves were calculated by the actuarial method of Kaplan and Meier. Differences between groups were analyzed by the generalized Wilcoxon test of Gehan. Prognostic factors were also studied using the multivariate technique of Cox.

RESULTS

Pathologic Features

Of the 27 patients originally identified, three were excluded because the diagnosis of malignant histiocytosis could not be confirmed; two patients were reinterpreted having non-Hodgkin's lymphoma, and one as a soft tissue histiocytoma.

Erythrophagocytosis was identified on histologic sections in six of the 24 cases and on smears or imprints in two others. Morphological findings of interest, based on lymph nodes from 19 cases, are summarized. Lymphocytes with atypical nuclei (atypical small lymphocytes) were found in 12 of the 19 and were prominent in three. Thick fibrous sclerotic bands were present to

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Hematopoietic Cell Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>63D3*</td>
<td>Promonocytes in bone, most peripheral monocytes, normal tissue histiocytes/macrophages</td>
</tr>
<tr>
<td>Anti-LeuM3†</td>
<td>Most peripheral monocytes, pleural/peritoneal phagocytic cells, normal tissue histiocytes/macrophages, Langerhans cells, monocytic leukemia</td>
</tr>
<tr>
<td>HLA-DR(α, L203)‡</td>
<td>B cells, monocytes/histiocytes, Langerhans cells, some activated T cells, some leukemia/lymphomas</td>
</tr>
<tr>
<td>Anti-Leu-1/Leu-4†</td>
<td>Thymocytes, T cells, T cell neoplasms, B-CLL (Leu-1)</td>
</tr>
<tr>
<td>Anti-Leu-6†</td>
<td>Thymocytes, Langerhans cells</td>
</tr>
<tr>
<td>Anti-Leu-9†</td>
<td>Subpopulation of T cells, some non-T/non-B (&quot;null&quot; cells), T cell leukemias/lymphomas</td>
</tr>
<tr>
<td>L3812‡</td>
<td>Panleukocytes</td>
</tr>
<tr>
<td>b, s§</td>
<td>B lymphocytes</td>
</tr>
</tbody>
</table>

* J. Donald Capra (Dallas, TX).
† Becton Dickinson (Mountain View, CA).
‡ Ronald Levy (Stanford, CA).
§ Coulter Clone (Hialeah, FL).

Table 2. Treatment Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Prophylactic IT-MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP or B-CHOP</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>CHOP or B-CHOP with high-dose methotrexate* with leucovorin rescue</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

*See text for description of regimens.
some degree in nine of the 19 cases, and in three, they were so marked as to give a strong resemblance to nodular sclerosing Hodgkin's disease. In all nine of these cases, the diagnosis of malignant histiocytosis was confirmed by findings in other biopsy specimens. Plasma cells were present in 15 of 19 cases and abundant in two. Eosinophils were found in only five cases, and in none were they a prominent feature. Reactive follicles were present in nine of 19 cases and were so numerous as to be a dominant feature in two, on low-power microscopy. Necrosis was unusual and was found focally in only four cases. Large, bizarre tumor cells with lobated or horseshoe-shaped nuclei, abundant cytoplasm, and occasionally prominent nuclear Hofs were present in 18 of the 19, and abundant in nine.

The results of frozen section immune histochemistry are reported in Table 3. One case expressed a mature monocyte/macrophage phenotype; three other cases were considered null cell or primitive lesions; and two cases were identified as probable T cell lymphomas. However, none of these cases were excluded from this analysis.

Clinical Characteristics

There were 24 patients with pathologically confirmed diagnoses of MH based on morphological criteria. The ages ranged from 17 to 87 years (median age, 28 years). There were 14 male and 10 female patients. Most patients presented with “B” symptoms (91%) and stage IV (80%). There were two stage II patients and three stage III patients. These patients all had nodal disease, with the exception of one stage II patient who also had pericardial disease documented by pericardiocentesis.

Multiple organ involvement was usual (see Table 4), including lymph nodes (21 patients), liver (15 patients), spleen (14 patients), lung (eight patients), bone marrow (six patients), skin (two patients), and CNS (one patient). Hepatic involvement was documented pathologically in six cases, but the liver was considered to be clinically involved if physical examination revealed a markedly enlarged liver, there was enlargement on liver-spleen scan, and liver function tests were abnormal. Splenic involvement was confirmed histologically in seven patients. Four patients underwent splenectomy at exploratory laparotomy, and three patients underwent a therapeutic splenectomy because of severe thrombocytopenia. The spleen was clinically considered to be involved if it was palpable. There were eight cases of pulmonary MH at presentation, which were associated with abnormal chest roentgenograms in each case. This included findings such as reticulo-nodular infiltrates or pleural effusions. Infectious etiologies were vigorously excluded in all eight cases. Three cases were pathologically confirmed by either lung biopsy or pleural fluid cytology. All pulmonary cases showed some improvement or resolution on chest roentgenogram after chemotherapy treatments. The bone marrow was involved in six of 22 bone marrow biopsies performed and in two of six bone marrow aspirates. There were two cases of MH presenting with skin involvement. In one patient, these lesions started as nonpruritic, macular, erythematous, blanching lesions, which later progressed to raised nodular lesions. The other patient had a similar rash but also had subcutaneous lesions. There was a low incidence of CNS involvement with only one positive lumbar puncture at presentation. Other sites at presentation included pericardium, bone, nasal and paranasal sinuses, and skeletal muscle.

Laboratory Findings

Nineteen patients were anemic (hematocrit <35 mg/100 mL) at presentation (75%) (Table 5). Thrombocytopenia (platelets <150,000/μL) occurred in 14 patients (58%), and leukopenia (WBC <3,000/μL)

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**Table 3. Immunologic Staining Results (Six Cases)**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Mature Leukocyte Markers (Leu-3, HLA-DR)</th>
<th>Mature Monocyte, Macrophage Determinants (Leu M3, 63D3)</th>
<th>T Cell Antigens (Leu-1,4,9)</th>
<th>Immunologic Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>Mature monocyte/macrophage</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>Null or primitive lesion</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>0</td>
<td>+ *</td>
<td>T cell proliferation</td>
</tr>
</tbody>
</table>

All six cases were unreactive for Leu-6 and B1.

*One case was reactive for Leu-4 and 9, another case was reactive only for Leu-9; these are anomalous phenotypes suggestive of T cell differentiation.
occurred in five patients (21%). Pancytopenia occurred in five patients, the exact same group of patients who were leukopenic. Leukocytosis (WBC > 10,000/μL), however, occurred in eight patients (33%). Although 15 patients presented with liver involvement (hepatosplenomegaly and/or documented liver infiltration), an abnormally elevated serum bilirubin (>2 mg/100 mL) was seen in only seven patients. One patient had a hemolytic anemia that was responsible for the elevated bilirubin, and erythropagocytosis was noted on this patient’s bone marrow aspirate. Serum lactate dehydrogenase (LDH) of >500 IU/dL was seen in eight patients.

**Treatment Results**

There are 22 evaluable patients who received systemic chemotherapy. Two patients died prior to treatment. Of the 22 treated patients, 15 had a CR (68%), five a PR (23%), and two had NR (9%). The median duration of CR was 30+ months (range, 9+ to 105+ months), and the median duration of PR was 2.4 months (range, 1–8 months). The median time to clinical CR was two cycles of chemotherapy. Of note is that the median duration of survival for patients who attained a CR has not been reached. The median duration of survival for the PR and NR group of patients was 3 months (range, 1–8 months). For the entire group of 24 patients, the median duration of survival was two years (Fig 1). There are seven long-term survivors alive >2 years. The five-year actuarial survival was 40%.

Three patients had undergone “therapeutic splenectomy” because of severe thrombocytopenia. One patient had a transient increase in platelet count, and the other two patients did not improve.

Of the 15 patients who attained a complete remission, five patients subsequently relapsed. The median time to relapse was 7.2 months (range, 1–13 months). Four patients relapsed systemically, with nodal, hepatic, cutaneous, and pulmonary involvement. There was one case of an isolated CNS recurrence, but this patient had presented initially with active CNS disease. One of the five relapsing patients has survived for 12 months without disease, while receiving a new combination chemotherapy regimen of VM-26, Ara-C, and cisplatin.

All patients who achieved a partial remission have died and have usually had widespread disease. Two developed CNS disease, which occurred in one patient despite prophylactic CNS therapy.

**Prognostic Factors**

Two factors were found to have independent statistical significance in predicting response to therapy and survival. They were: (1) an initial platelet count <150,000 (P Gehan = .0003, P Cox = .005), and (2) the dose of drug delivered (P Gehan = .0034, P Cox = .057). Factors not found to be statistically significant in predicting for survival were age, sex, stage of disease, the presence of “B” symptoms, specific disease site at presentation, WBC, serum bilirubin, serum LDH, whether or not bleomycin or prophylactic CNS therapy were given, or whether splenectomy was performed (Table 6). Of interest is that at 3.5 years from the time of diagnosis, patients who received midcycle HD-MTX with leucovorin rescue have a higher survival rate (50% v 30%). However, this was not statistically significant (P Gehan = .3). Although many factors were not statistically significant for predicting

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**Table 5. Laboratory Findings at Presentation**

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Percent</th>
</tr>
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<tbody>
<tr>
<td>Anemia (Hct &lt; 35 mg/100 mL)</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>Thrombocytopenia (platelets &lt; 150,000 cells/μL)</td>
<td>14</td>
<td>58</td>
</tr>
<tr>
<td>Leukocytosis (WBC &gt; 10,000 cells/μL)</td>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>Elevated LDH (&gt;500 IU/dL)</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Bilirubin (&gt;2 mg/dL)</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Leukopenia (WBC &lt; 3,000/μL)</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>5</td>
<td>21</td>
</tr>
</tbody>
</table>

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**Fig 1. Kaplan-Meier survival analysis for 24 patients with MH.**

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**Table 6. Results of Univariate and Multivariate Analysis**

<table>
<thead>
<tr>
<th>Significant</th>
<th>P (Gehan)</th>
<th>P (Cox)</th>
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<tbody>
<tr>
<td>Platelet count &lt;150,000</td>
<td>.0003</td>
<td>.009</td>
</tr>
<tr>
<td>Dose of drugs delivered</td>
<td>.0034</td>
<td>.057</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not significant</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>B symptoms</td>
<td></td>
</tr>
<tr>
<td>Disease site</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td></td>
</tr>
<tr>
<td>Bilirubin level</td>
<td></td>
</tr>
<tr>
<td>Bleomycin</td>
<td></td>
</tr>
<tr>
<td>Prophylactic CNS therapy</td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td></td>
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</table>
treatment outcome, it should be emphasized that the total patient population is small, and only two covariates could be analyzed simultaneously.

**Response According to Platelet Count**

The response to therapy according to the initial platelet count was analyzed. There were 14 patients who had an initial platelet count >150,000 cells/μL. Twelve of these patients (86%) attained a CR, and ten surviving patients are still free of disease. There were two PRs in this group, and these patients ultimately died of disease.

In contrast, there were ten patients who had an initial platelet count <150,000 cells/μL. This subgroup of patients did poorly in comparison. There were only three CRs (30%), with only one surviving patient. Of the remaining seven patients, there were three PRs, two who did not respond, and two patients who did not receive therapy. All of these patients died of progressive disease. In this poor prognostic group, six patients had dose reductions of chemotherapy of up to 50% or were treated with nonmyelosuppressive drugs. The majority of these patients had both spleen and bone marrow involvement with MH.

Figure 2 displays the marked difference in survival according to the initial platelet count.

**DISCUSSION**

The purpose of this study has been to summarize the clinical findings in 24 patients with MH and their response to combination chemotherapy using Adriamycin. The observed clinical and laboratory findings at presentation are similar to previously reported series. In this study, the most common extranodal site of involvement was the lung. We found a 33% radiographic incidence of pulmonary parenchymal involvement at presentation, which is similar to the findings of Rilke et al and Dunnick et al. Radiologic features were generally nonspecific, with most patients having bilateral reticulonodular or fluffy infiltrates, and rarely nodules. These findings are similar to those reported by Colby et al.

In 1977, Alexander and Daniels reported a series of 16 patients with MH, including seven patients in this series, in which several CNS relapses occurred. Based on these observations, it was recommended that CSF cytology should be part of the initial evaluation, and that CNS prophylaxis be considered for patients achieving CR. Other authors have published case reports of meningeal and cerebral involvement with MH. We have observed a very low incidence of CNS disease at presentation, and no apparent difference in survival for those patients who received prophylactic intrathecal therapy. Two patients who did not attain a CR subsequently developed CNS involvement. Only one patient developed an isolated CNS relapse that occurred after a CR. This patient, however, initially presented with CNS disease.

There have been a number of reports in the literature of the treatment of MH using Adriamycin-based chemotherapy. The three largest series have used CHOP chemotherapy, with CR rates ranging from 57% to 92%. The numbers of treated patients, however, were small and the duration of follow-up short. Our response rate is similar (68% CR). Long-term survival is possible, as we have obtained a 40% 5-year actuarial survival.

The addition of midcycle HD-MTX with leucovorin rescue to CHOP chemotherapy has resulted in an improved absolute survival at 3.5 years. It is theoretically reasonable to add this agent at midcycle because MH is a kinetically aggressive neoplasm. However, we realize that the number of treated patients is small and statistically we have not yet demonstrated a survival benefit. The addition of bleomycin did not influence survival.

Thrombocytopenia was found to be the most significant prognostic factor in predicting survival. Of ten patients who presented with thrombocytopenia (platelet count <150,000 cells/μL), there were only three patients who attained a CR and only one who is currently surviving. Dose reduction of chemotherapy was the second most significant factor in predicting for survival and was statistically independent from the platelet count. We would now recommend that aggressive chemotherapy (at 100% calculated doses) be given despite thrombocytopenia.

Most patients attained a CR within two cycles of chemotherapy. If a CR is not attained after two to three cycles, we would recommend using a different regimen with non-cross-resistant agents. Although anecdotal, other active agents include the epipodophyllotoxins, cytosine arabinoside, cisplatin, procarbazine, vinblastine, and nitrogen mustard. We have
achieved a second durable response in one patient using a VM-26, Ara-C, and cisplatin salvage regimen.

Immunophenotyping may allow distinction of MH from other malignant lymphomas and may help to identify subgroups of histiocytic malignancies that have clinical and prognostic differences. In this series, we have identified two cases that probably represent T cell lymphomas and were histologically indistinguishable from the other cases. The cases are most likely similar to those reported by Kadin et al.7 One patient is alive on chemotherapy at 12+ months; the other patient died approximately 2 months after diagnosis.

Based on the data presented here, our new therapeutic approach for malignant histiocytosis includes: (1) initial chemotherapy with CHOP, using midcycle HD-MTX at a dose of 1 g/m² over a 30-minute infusion with leucovorin rescue; (2) CSF cytology as part of the initial evaluation, but no routine use of CNS prophylaxis (cranial irradiation or intrathecal MTX); (3) full doses of chemotherapy with aggressive supportive care; and (4) built-in crossover to noncross-resistant chemotherapy if a CR is not attained after two drug cycles.

REFERENCES

The treatment of malignant histiocytosis

A Jr Tseng, CN Coleman, RS Cox, TV Colby, RR Turner, SJ Horning and SA Rosenberg