Effectiveness of Methyl-GAG (Methylglyoxal-bis[Guanylhydrazone]) in Patients With Advanced Malignant Lymphoma

By Raymond P. Warrell, Jr., Burton J. Lee, Sanford J. Kempin, Mortimer J. Lacher, David J. Straus, and Charles W. Young

We treated 51 patients with advanced malignant lymphoma refractory to conventional therapy with methylglyoxal-bis[guanylhydrazone] (methyl-GAG) at doses ranging from 400 to 800 mg/m². Therapy was started on a weekly schedule and was switched to every other week in responding patients at the onset of toxicity. Partial responses were observed in 6 of 13 evaluable patients with Hodgkin’s disease (46%), 5 of 10 patients with diffuse poorly differentiated lymphocytic lymphoma (50%), 2 of 4 patients with nodular poorly differentiated lymphocytic lymphoma (50%), and 3 of 13 patients with diffuse histiocytic lymphoma (23%). Two of six patients with mycosis fungoides showed objective improvement in cutaneous disease. Toxicity was generally mild and included muscular weakness, myalgia, mucositis, and diarrhea; two patients developed bronchospasm following drug infusions. We conclude that methyl-GAG has major antitumor activity when administered on this schedule to patients with advanced malignant lymphoma. The low degree of toxicity, unique mechanism of action, and minimal myelosuppressive effects suggest that methyl-GAG will prove useful in future trials of combination chemotherapy regimens for the treatment of lymphoma.

Methylglyoxal-bis[guanylhydrazone] (methyl-GAG) was one of several synthetic polyfunctional hydrazones initially reported to have antitumor activity by Freedlander and French in 1958. While its exact mechanism of action remains unclear, methyl-GAG interferes with polyamine biosynthesis via inhibition of S-adenosylmethionine decarboxylase. Several other biologic effects have been observed, including binding to DNA and action as a mitochondrial poison.

Early clinical trials using a daily dose schedule revealed impressive antitumor activity; however, this was associated with prohibitive toxic reactions that included fatal hypoglycemia, profound myelosuppression, and severe cutaneous or gastrointestinal ulcerations. Thereafter, except for occasional reports, clinical interest was limited until the Southwest Oncology Group reported acceptable toxicity in a phase I trial that employed a weekly infusion schedule. Although this latest study noted no responses in six patients with lymphoma, methyl-GAG had demonstrable antilymphoma activity in earlier, daily-dose trials. Therefore, we evaluated this drug employing a weekly schedule in patients with advanced malignant lymphoma refractory to conventional treatment.

PATIENTS AND METHODS

Fifty-one patients with Hodgkin’s disease, non-Hodgkin’s lymphoma, and mycosis fungoides who had failed conventional therapy were entered into this study. The treatment protocol required histologic confirmation of disease, life expectancy >4 wk, performance status ≤50 ( Karnofsky), and adequate renal and hepatic function (serum bilirubin and creatinine ≤1.5 mg/dl); patients must not have received radiation or chemotherapy within the 3 wk preceding entry. Requirements for normal pretreatment hematologic status were dropped after initial data showed minimal myelosuppression. Except for 4 of the 6 patients with mycosis fungoides, all patients had bidimensionally measurable disease parameters. Pretreatment evaluation included history and physical examination, complete blood and platelet count, serum biochemical screening profile, and chest roentgenogram. Additional procedures were performed as needed to assess the extent of disease. All patients gave signed, informed consent and the study was approved in advance by the Clinical Investigations Committee of the Memorial Sloan-Kettering Cancer Center.

Response Criteria

A complete response was defined as the complete disappearance of all evidence of disease and normalization of all biochemical parameters for >4 wk; in addition, a complete response required limited restaging, which included as a minimum a bone-marrow biopsy (if initially involved with disease) and an abdominal computed tomographic scan. A partial response was defined as >50% decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions without the appearance of new lesions for at least 4 wk. Tumor regressions of <50% or <4 wk duration were recorded as failures. Duration of response was defined from the date a >50% response was observed to the date of evident disease progression.

Toxicity Criteria

Mucositis was graded as follows: 1+, objective oral ulcerations without impairment of oral intake; 2+, impaired ability to eat or drink; 3+, hospitalization required to avoid dehydration from extensive mucositis. Myopathy was graded as 1+, generalized fatigue

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without objective signs of myopathy; 2+, objective muscular weakness (e.g., difficulty arising from chairs, decreased muscle strength on physical examination); 3+, severe muscular weakness requiring hospitalization.

**Method of Administration**

After reconstitution of the drug with normal saline, the prescribed dose of methyl-GAG was further diluted in 250 ml of 5% dextrose solution and infused intravenously over 60–90 min. The initial weekly dose of methyl-GAG was 600 mg/sq m for patients with normal pretreatment blood counts, PS ≥60, and no history of abdominal radiation; this dose was attenuated by 100 mg/sq m for patients not meeting these criteria. In the absence of toxicity [1+ mucositis, 2+ myopathy, or myelosuppression (WBC < 3000/cu mm or platelets < 100,000/cu mm) not related to myelophthisis], subsequent doses were escalated by 100 mg/sq m/wk until such toxicity was observed. At the onset of toxicity, treatment was withheld for 10–14 days and reinstated in responding patients on a biweekly schedule. Patients were considered adequately treated and evaluable for response after receiving 2 doses of methyl-GAG, with or without toxicity.

**RESULTS**

Between January and August 1980, 51 patients with advanced malignant lymphoma were entered into this study. Pretreatment characteristics of these patients are presented in Table 1. [A “course” of chemotherapy is defined as a single drug used alone (e.g., a phase II agent) or several drugs used in combination for at least 4 wk (e.g., MOPP: mechlorethamine, vincristine, procarbazine, prednisone).]

Excluding the 6 patients with mycosis fungoides, all patients had been extensively treated with combination chemotherapy; 19 patients had already failed one or more investigational drugs. Forty patients had also received radiotherapy. Except for 2 patients with non-Hodgkin’s lymphoma, all other patients had stage IV disease (Ann Arbor classification). Thirty-six of these 45 patients had either liver, lung, or bone marrow involvement with disease. Other involved sites included kidney, pericardium, cerebrospinal fluid, muscle, prostate, vagina, and breast (one patient each). Five patients had skin involvement and two had disease in cortical bone. The median dose of methyl-GAG administered was 600 mg/sq m (range 400–800 mg/sq m); the median number of doses administered per patient was 3 (range 1–20+).

**Therapeutic Effects**

Of the 51 patients entered into the study, 46 are evaluable for response. After careful restaging, no patient was considered to have had a complete response. As shown in Table 2, the overall partial response rate for patients with non-Hodgkin’s lymphoma was 37%. While responses were noted in all histologic subtypes, the observed rate of response was lower in patients with DHL. Although 3 patients with end-stage DPDL and lymphosarcoma cell leukemia were entered with lower than minimally acceptable performance status, they have been included in the analysis as evaluable and not responding.

Six of 13 evaluable patients with Hodgkin’s disease (46%) also showed partial responses. The median duration of response for all patients with lymphoma was 3 mo (range, 1–11+ mo). In addition, 2 of 6 patients with mycosis fungoides showed objective improvement in cutaneous disease for 4 mo duration. Most responses occurred rapidly; the median time required to achieve a partial response in all disease categories was 2 wk (range, 1–6 wk).

Five patients were excluded from the above analysis for response. Two patients (with NPDL and DHL, respectively) developed bronchospasm following their first and second doses of methyl-GAG, which required their removal from the study. The patient with NPDL showed complete disappearance of disease after one dose, but relapsed 3 wk later. The patient with DHL showed major symptomatic improvement but his measurable disease was unchanged. One additional patient with NPDL refused further therapy after 1

**Table 1. Pretreatment Characteristics of Patients With Malignant Lymphoma Treated With Methyl-GAG (n = 51)**

<table>
<thead>
<tr>
<th>Pretreatment Characteristics</th>
<th>Median Age (range)</th>
<th>Median Performance Status (Karnofsky)</th>
<th>Median Number of Previous Chemotherapy Courses (range)</th>
<th>Median Number of Previous Chemotherapeutic Agents (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s disease</td>
<td>15</td>
<td>70 (40–90)</td>
<td>3 (1–7)</td>
<td>8 (4–12)</td>
</tr>
<tr>
<td>Diffuse histiocytic (DHL)</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse poorly differentiated lymphocytic (DPDL)</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodular poorly differentiated lymphocytic (NPDL)</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sites of extranodal involvement</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>13/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung/pleura</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data exclude patients with mycosis fungoides.

**Table 2. Response Rates of Patients With Malignant Lymphoma Treated With Methyl-GAG**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Patients Responding</th>
<th>Patients Evaluable</th>
<th>Response Rate</th>
<th>Duration of Response (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s disease</td>
<td>6</td>
<td>13</td>
<td>46%</td>
<td>8.5, 4.5, 4, 3.5, 2, 1</td>
</tr>
<tr>
<td>DHL</td>
<td>3</td>
<td>13</td>
<td>23%</td>
<td>7.5+, 3, 1</td>
</tr>
<tr>
<td>DPDL</td>
<td>5</td>
<td>10</td>
<td>50%</td>
<td>11+, 2, 2, 2, 1, 1, 1, 1</td>
</tr>
<tr>
<td>NPDL</td>
<td>2</td>
<td>4</td>
<td>50%</td>
<td>8+, 3</td>
</tr>
</tbody>
</table>
dose because of excessive fatigue despite >50% reduction of his measurable disease (also for 3 wk duration). Two patients with Hodgkin’s disease were excluded because of major protocol violations (concurrent administration of other chemotherapy or radiation).

Toxicity

The toxic effects of methyl-GAG encountered during this study are presented in Table 3. All patients experienced transient facial paresthesiae or flushing during the drug infusion; this effect could be substantially ameliorated by prolonging the duration of the infusion. The most significant (and dose-limiting) toxicity was muscular weakness, frequently accompanied by myalgia. This effect appeared in mild form after 2–3 doses and worsened with continued treatment on a weekly schedule. Although most patients complained of excessive fatigue, only 9 patients developed objective signs of myopathy. Serum levels of creatine phosphokinase in 2 of these patients were normal. Although muscle biopsy, electromyogram, and nerve conduction studies were not performed on our patients, these studies were normal in 2 other patients who developed 3+ weakness while receiving methyl-GAG in a separate trial (R. Chapman, unpublished data). The weakness generally resolved after 2 wk off therapy and did not recur when patients were switched to a biweekly dose schedule.

Gastrointestinal toxicity was mild and nausea was usually limited to the period of drug infusion. Mucositis was seen in 13 patients, but this interfered with eating in only one individual who simultaneously had developed renal insufficiency from disease progression. Skin toxicity included diffuse truncal erythema in two patients and localized maculopapular eruptions in three patients. As noted previously, two patients experienced bronchospasm that required their removal from study; this reaction has not been previously reported. One of these patients was rechallenged with 50 mg of methyl-GAG and again developed wheezing. One patient has developed a sideroblastic anemia; at present it is unclear whether this is drug-related or if it represents the early appearance of a second hematologic cancer. There was no clinical or biochemical evidence of hypoglycemia during this trial.

Myelosuppression was minimal, as assessed in the 28 patients who were neither leukopenic nor thrombocytopenic before treatment (WBC ≥ 4000/cu mm, platelets ≥ 150,000/cu mm). The median WBC count at the lowest point on study for these patients was 5000/cu mm (range, 2100–17,500); the median platelet nadir was 207,000/cu mm (range, 16,000–658,000). The broad range of these counts, however, suggests that methyl-GAG produces more significant myelosuppression in patients with diminished bone marrow reserves.

DISCUSSION

Despite improved results in the treatment of malignant lymphoma, at least 50% of patients with advanced DHL die with progressive disease, and an equal proportion of patients presenting with advanced-stage Hodgkin’s disease fail or relapse from primary MOPP-chemotherapy. Furthermore, treatment-related complications (including sterility and possibly leukemogenesis) represent increasing problems for those patients who achieve prolonged survival. Thus, there exists a continuing need to identify active agents that can equal or improve current therapeutic results with reduced toxicity.

Because of high initial response rates achieved with conventional chemotherapy protocols, however, patients with lymphoma become eligible for treatment with investigational drugs only after intensive prior therapy. Moreover, limiting this treatment to relapsed patients undoubtedly selects a population with inherently more aggressive disease, which may already be resistant to multiple chemotherapeutic agents. Despite these difficulties, we have demonstrated substantial antilymphoma activity for methyl-GAG used singly even in patients with disease progression after the use of multiple conventional (and several investigational) drugs. While acknowledging the hazards of comparing different patient populations, it should be noted that both the rate and duration of responses observed for methyl-GAG in this trial compare favorably with results reported for other single agents of proven efficacy in lymphoma, including adriamycin and bleomycin.

Toxic reactions encountered during this trial were generally mild; this probably resulted from changing from a weekly to a biweekly schedule in responding patients at the onset of toxicity. Less than 25% of our
patients tolerated as many as 4 consecutive weekly doses; for this reason, we currently give only 2 weekly doses, with biweekly administration thereafter. On this schedule, the drug has a high degree of patient acceptability, especially for individuals receiving long-term therapy. It is by no means certain that this dose schedule optimizes the therapeutic index for this drug. Since recent data suggest prolonged urinary excretion (>7 days) and drug accumulation when given on a weekly basis, further exploration of alternative dose schedules may be desirable.

Methyl-GAG probably exerts its major cytotoxic effects via inhibition of polyamine synthesis, since these effects can be abolished in vitro by the simultaneous administration of the polyamine spermidine. Therefore substances that inhibit the rate-limiting enzyme in the synthetic pathway, ornithine decarboxylase, and related substances. Biochem J 139:351-357, 1974

Methyl-GAG probably exerts its major cytotoxic effects via inhibition of polyamine synthesis, since these effects can be abolished in vitro by the simultaneous administration of the polyamine spermidine. Therefore substances that inhibit the rate-limiting enzyme in the synthetic pathway, ornithine decarboxylase (ODC), might enhance the antitumor effectiveness of methyl-GAG. We have recently demonstrated such synergy in mice with L1210 leukemia using methyl-GAG and the trypanocidal compound, α-difluoromethylornithine, which blocks formation of putrescine via inhibition of ODC. This clinical finding of methyl-GAG's efficacy in lymphoma should initiate further investigation into the role and therapeutic manipulation of polyamine metabolism in neoplastic disorders.

We conclude that methyl-GAG has substantial activity in lymphoma, even in heavily pretreated patients with advanced disease. Its apparently unique mechanism(s) of action and minimal myelosuppressive activity in the schedule described makes this drug very attractive for further investigation, both as a single agent and in combination chemotherapy programs.

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