Phase 2 Study with Baker’s Antifol in Solid Tumors


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SUMMARY

One hundred thirty-eight adults with advanced cancers were treated with Baker’s Antifol. The complete response + partial response rate was only 10%. Best responses were obtained in 31 patients with lung adenocarcinoma (complete response + partial response, 13%), in 25 patients with colorectal carcinoma (partial response, 16%), and in 6 patients with renal cell carcinoma (partial response, 50%). Two partial responses occurred in 15 patients with squamous cancer. No significant responses were seen in 27 patients with other adenocarcinomas, 13 with sarcomas, 14 with melanomas, and 8 with miscellaneous tumors. The most frequent toxicities were dermatitis, stomatitis, gastrointestinal symptoms, and mild myelosuppression. The incidence of dermatitis was significantly decreased by shortening the schedule of Baker’s Antifol administration from 5 to 3 days. Baker’s Antifol has some degree of antitumor activity, and studies of combination of this agent with other effective chemotherapeutic agents are indicated.

INTRODUCTION

BAF3 or triazinate is a triazine folate antagonist that, like MTX, inhibits dihydrofolate reductase but differs from MTX in its mode of action. While active enzymatic transport is required for MTX to penetrate the cell membrane, it is not required for BAF (1). One mechanism of resistance to MTX is lack or loss of membrane transport. Thus, BAF can potentially have therapeutic activity in those tumors where MTX might not be active or where high doses of MTX are needed. Early Phase I studies with BAF demonstrated that there is biological activity in humans at total doses of about 500 to 750 mg/sq m (4, 5). Our own Phase I trial in patients with advanced malignant diseases suggested that this drug had an antitumor effect at daily dosages of 150 mg/sq m administered for 5 days (4). With these dosages, various side effects were seen, mainly dermatitis, mucositis, and myelosuppression. However, therapeutic efficacy was observed in some patients with solid tumors, particularly adenocarcinomas. Consequently, a Phase II study of BAF was conducted at our institution in patients with advanced solid tumors.

MATERIALS AND METHODS

Patients with advanced solid tumors, preferably those with metastatic adenocarcinomas, squamous carcinomas, sarcomas, and melanomas, were eligible for this study. To qualify for therapy with BAF, patients had to be considered refractory to prior therapy and not eligible for other modalities of therapy of higher priority. If the patients had received prior therapy, they must have recovered from the toxicity of the previous treatment. Patients who had received prior therapy with MTX were also eligible to enter the study. Patients were required to have adequate renal function (blood urea nitrogen less than 25 mg/dl, creatinine less than 1.5 mg/dl) and adequate liver function (bilirubin less than 1.5 mg/dl; serum glutamic oxaloacetic transaminase, less than 50 units; alkaline phosphatase less than 200 units). However, 13 patients with some degree of liver dysfunction that was attributed to metastatic tumor were accepted in the study.

The starting dose of BAF was 150 mg/sq m/day for 5 days administered as an i.v. infusion over a 1-hr period. The interval between courses was 2 to 3 weeks. In patients with liver dysfunction, the starting dose was reduced to 100 mg/sq m daily for 5 days. After the 1st 31 patients had been entered in the study, the schedule of administration was changed to 250 mg/sq m daily for 3 days in patients with normal liver function, or 150 mg/sq m daily for 3 days in patients with abnormal liver function. This change in the schedule of administration was made after it became evident that a substantial number of patients developed dermatitis on Days 5 to 7 of therapy. It was postulated that by modifying the schedule of administration, the normal cells would be exposed for a shorter time to the drug and toxicity could be reduced; thus, an attempt was made to deliver the same total dose in a shorter period of time. The drug was dissolved in 100 to 200 ml of dextrose solution and infused i.v. in 1 to 2 hr. If no significant toxicity occurred, the dose was increased or decreased by 50 mg in subsequent courses. Informed consent was obtained from all patients, according to institutional policy. The disease status of each patient was carefully evaluated prior to initiation of therapy and before each 1 or 2 courses. Measurable lesions and any changes in these lesions were recorded. Complete response was considered to have occurred when all evidence of disease disappeared and the patient returned to the normal status of well being. Partial response was considered when tumor regression occurred that was greater than 50% of the sum of the products of the 2 largest diameters of measurable lesions. Tumor regression of less than 50% or

1 Supported in part by Contract NO-1-CM57042 and Grants CA 05831 and 11520 from the National Cancer Institute, NIH, USPHS, Bethesda, Md. 20014.
2 To whom requests for reprints should be addressed.
3 The abbreviations used are: BAF, Baker’s Antifol or triazinate (ethanesulfonic acid compound with a-[2-chloro-4-[4,6-diamino-2,2-dimethyl-s-triazine-1(2H)-yl](phenoxyl)-N,N-dimethyl-m-toluamide]; MTX, methotrexate; MER, methanol extraction of phenol-killed tubercle bacilli.

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cessation of previously progressive disease during therapy was considered stable disease if it lasted for 8 weeks or longer. Patients who responded to BAF continued to receive courses of therapy at the maximally tolerated dose every 2 to 3 weeks until disease progression or relapse was observed.

Complete blood counts with differential and platelet count, SMA 100, and radiographic studies as indicated were done in all patients prior to therapy. Complete blood counts were repeated in most patients at least once a week; SMA 100 was repeated in most patients at least once before each course of therapy; radiographic studies were repeated as clinically indicated. Tumor measurements were made prior to each course of therapy. The duration of response of the patients of this study was considered from the time they achieved response. The duration of survival was measured from the time the patients entered the study.

**RESULTS**

One hundred forty-two patients were entered in this study from July 1974 through October 1975. Four patients who died of rapidly progressing disease within 1 week after treatment (2 melanomas and 2 adenocarcinomas) were considered early deaths.

The 138 evaluable patients also include 49 consecutive patients that, in addition to BAF, also received MER and who were entered while the Phase I study of immunotherapy with MER was conducted (3). However, since no differences in response or survival attributable to MER were observed, these 49 patients were analyzed with the whole group.

The 138 evaluable patients ranged in age from 17 to 82 years (median, 52 years). Seventy-three were males and 65 were females. All patients had metastatic cancers, as listed in Table 1, and most had received and were refractory to prior chemotherapy with cyclophosphamide, 5-fluorouracil, Adriamycin, or nitrosoureas, alone or in combination. Thirty-eight patients had also received MTX as prior therapy. Thirty-one patients with adenocarcinoma of the lung had received no prior chemotherapy.

The results in this study were analyzed in accordance with the schedule of administration and prior therapy (Table 2). The response was complete or partial in only 9%. In addition, in 21% of the patients responses <50% or stabilization of disease occurred. The overall response (complete + partial) in the 31 patients receiving BAF with the 5-day schedule was 6% compared to 10% in the 107 patients receiving the 3-day schedule. No complete response and only 2 partial responses occurred with the former schedule, compared with 1 complete response and 10 partial responses with the latter. The proportions of patients with stable disease were 39 and 18%, respectively. The response rate was 21% in the 33 patients receiving no prior therapy, compared with 6% in the patients receiving prior therapy. Considering only those patients who had received prior therapy, the response rates were not significantly different between the 38 patients who had received prior MTX and the 67 who had not.

The therapeutic effects of BAF in the various cancers of the patients in this study are shown in Table 3. Best responses were obtained in patients with lung adenocarcinoma who had a complete plus partial response of 13% and in 25 patients with colorectal adenocarcinoma with a response rate of 16%. In 6 patients with renal cell carcinoma, there were 3 partial responses (50%). Stabilization of disease was seen in most tumor categories.

The responses in the 15 patients with squamous cell carcinoma are also shown in Table 3. Two patients achieved a partial response and in 2 there was stabilization of disease. Two partial responses occurred in 1 of 7 patients with head and neck cancer and 1 of 2 patients with unknown primary. In 13 patients with sarcoma, there were only 3 with stable disease, one of 3 patients with osteosarcoma, and 2 of 10 with soft tissue sarcoma. There were only 2 patients with disease stabilization in the 14 patients with malignant melanoma, and 1 with disease stabilization (oat cell carcinoma) in the 7 with miscellaneous tumors.

The median duration of complete and partial response for the patients in this study was 14 weeks (range, 4 to 56 weeks). The median duration of survival for all patients entered was 24 weeks. The most frequent toxicities occurring with BAF were dermatitis, stomatitis, gastrointestinal symptoms, and myelosuppression. The clinical characteristics of these side effects have been described (4). The

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<tr>
<td><strong>BAF Phase 2</strong></td>
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<tr>
<td>Type of neoplasia</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Squamous cell</td>
</tr>
<tr>
<td>Melanoma</td>
</tr>
<tr>
<td>Sarcoma</td>
</tr>
<tr>
<td>Miscellaneous*</td>
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<td><strong>Total</strong></td>
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* Two thyroid, 2 oat cell, 1 bladder, 1 mixed lymphoma, and 2 undifferentiated, site unknown.

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<td><strong>Response to BAF</strong></td>
</tr>
<tr>
<td>Category</td>
</tr>
<tr>
<td>Schedule 1*</td>
</tr>
<tr>
<td>Schedule 2*</td>
</tr>
<tr>
<td>Prior therapy</td>
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<tr>
<td>No prior therapy</td>
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* 150 mg/sq m/day for 5 days.
* 250 mg/sq m/day for 3 days.
incidence of dermatitis in this study decreased significantly ($p = 0.002$) with the shortening of the schedule of administration (Table 4). However, other types of toxicity were not significantly reduced. Dermatitis in a patient with renal cell carcinoma progressed after 2 doses of BAF to generalized epidermal toxic necrolysis which contributed to death. Postmortem examination in this patient also showed generalized intestinal ulcerations and bone marrow hypoplasia. Myelosuppression occurred in 30% of the patients and mostly in patients developing also dermatitis and mucositis. Leukopenia and thrombocytopenia were well tolerated and rapidly reversible (within 5 days) in most patients. Severe infection during leukopenia occurred in 5 patients, all of whom responded to antibiotic therapy. Dermatitis, stomatitis, and myelosuppression occurred mainly in patients with liver dysfunction. Fever and occasionally chills with the administration of BAF were observed in 4 patients; no hemorrhagic complications occurred. Two patients with history of previous radiotherapy to the head and neck experienced erythematous rash at the site of the radiation during administration of BAF. Nausea, vomiting, and/or diarrhea were experienced in 6 patients. One patient who had received 2 previous courses of therapy died of respiratory distress that occurred shortly after completing a dose of BAF during the 3rd course of therapy outside of the institution. Unfortunately, an autopsy was not performed.

DISCUSSION

The results of this study indicate that BAF has some degree of activity in various solid tumors. However, the most encouraging results in this study were those in adenocarcinoma of the lung and renal cell carcinoma. No drug has been identified yet that is very efficacious in these diseases. Therefore, it appears that it is worthwhile to explore this agent in combination or in different schedules in the therapy of these solid tumors. The responses in squamous carcinoma were modest and of little benefit in sarcoma and melanoma. Nevertheless, this drug could be explored further in combination regimens.

The attractiveness of BAF in chemotherapy derives from its ability to penetrate the cell membrane without an active enzymatic transport. This property theoretically should make the drug effective in those tumors that are MTX resistant or that have become refractory to MTX (1). Whether this is true clinically or not is impossible to ascertain from this study. However, it is interesting to observe that in those
patients who had received prior therapy the response of those receiving prior MTX was not inferior to the response of those receiving other agents.

The pharmacology of BAF indicates that the drug is excreted by the liver (2, 5). Also, our initial clinical trials indicated that toxicity with BAF was accentuated in patients with liver dysfunction (4). In this study, the toxicity to the skin and mucosa was significant initially and, thus, the duration of therapy was reduced to 3 days, although the total dose per course remained the same. The half-life of BAF is approximately 6 hr, so it was postulated that by reducing the exposure of the normal cells to the compound, one could decrease the toxicity. This was also indicated because dermatitis and stomatitis usually appeared on Day 5 to 7 of a course of BAF. We were able to reduce the dermatological toxicity (which may be dose limiting) in our patients significantly by shortening the duration of administration to 3 days. However, the incidence of other toxicity was not significantly altered. Major toxicities in this study occurred in patients with liver function abnormalities, as has been described previously (4).

Our studies suggest that BAF has some antitumor activity for the management of certain cancers; studies of the combination of this agent with other effective chemotherapeutic agents should be done. The drug has toxicity that is more severe for those patients who have liver dysfunction. It is possible that toxicity could be reduced or avoided by using citrovorum factor following the administration of BAF. This approach is currently being explored in our institution.

REFERENCES

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