Phase II Clinical Trial of a Murine Monoclonal Antibody Cytotoxic for Gastrointestinal Adenocarcinoma

Henry F. Sears, Dorothee Herlyn, Zenon Steplewski, and Hilary Koprowski


ABSTRACT

A murine monoclonal antibody (MAb) which binds to human metastatic gastrointestinal adenocarcinomas can be administered safely and has tumor effects in some patients. Its therapeutic effect was assessed in 20 patients with measurable advanced colorectal carcinoma that was refractory to prior surgical resection, chemotherapy, and/or radiotherapy. All patients had agreed to receive no other therapy at the time of MAb administration and follow-up evaluation. In one patient, tumor at all known sites responded after a single i.v. injection of antibody. One other patient had a marked reduction in a hepatic metastasis where binding of 131I-labeled F(ab')2 MAb fragments was demonstrated but not in his abdominal wall metastases where no MAb binding could be demonstrated. In a third patient, stabilization persisting for 12 mo of an aggressively growing tumor was observed. The antibody was well tolerated in all patients, although 10 patients mounted an anti-murine immunoglobulin antibody response.

INTRODUCTION

Immunotherapy of gastrointestinal adenocarcinoma with murine MAb is a new approach to the management of a difficult clinical problem. Previous in vitro and animal in vivo studies have identified a murine IgG2a MAb 1083-17-1A (17-1A) that has strong cellular effector-mediated cytotoxicity and gastrointestinal tumor inhibitory properties (1–3). Preliminary clinical trials in patients to assess toxicity and binding specificity of this MAb indicated the safety of a single systemic exposure to this murine immunoglobulin, the human response to mouse immunoglobulin as antigen, and the possibility of allergic reactions to multiple antibody infusions (4, 5). The studies also indicated tumor responses in some patients (4, 5). In those patients, biopsy-proven tumor regression was temporarily associated with the administration of antibody and 2 of the 20 patients have remained tumor-free for more than 2 yr. Evaluation of antibody specificity in that trial could be done only after biopsy obtained during operative management of metastatic disease and some indicator lesions were thereby altered. Furthermore some of the patients had either stopped chemotherapy just prior to or after entering the immunotherapy trial and one patient received radiation therapy 6 wk after antibody administration, despite the fact that his circulating tumor antigen (carcinoembryonic antigen) levels had already returned to normal.

The present clinical study was conducted to evaluate the effects on MAb 17-1A in a patient population with large tumor burden but without potentially confounding factors such as simultaneous additional forms of therapy. Findings in this trial support a role for MAbs as tumor modulators and suggest the need for modified strategies in antibody administration.

MATERIALS AND METHODS

Patients. Patients with advanced colon and rectal carcinomas were included in this study if they had a 3-mo expected survival, a lesion proven refractory to conventional therapies, a measurable lesion on chest X-ray, liver scan, or computed tomographic evaluations, no other therapy for at least 1 mo prior to mouse MAb administration, no hepatic dysfunction as reflected by bilirubin or serum glutamic oxaloacetic transaminase levels less than twice normal levels, no renal dysfunction, and no other cytotoxic therapy during the 3-mo evaluation phase of the study. A total of 20 patients were included in this study between January and September 1983 with informed consent from each patient. If evidence of disease progression was observed at any time after the start of the evaluation, the patient was treated by the appropriate conventional modalities as determined by the referring physician. The measurable lesions were studied at 1 and 3 mo after antibody infusion by the same technique used for the initial evaluation. Blood studies were done to assess potential hematological, renal, or hepatic toxicity, and to detect immune responses stimulated by murine immunoglobulin.

Antibody. The IgG2a murine monoclonal antibody 17-1A was derived from mice immunized with SW1083 human colon carcinoma cells (6, 7). The antibody was purified from hybridoma cell culture supernatants or from ascites of hybridoma tumor-bearing mice by Protein A-Sepharose column chromatography. The effluent of the column was tested for Gram-negative endotoxins by the Limulus ameboocyte lysate assay. Purity of the immunoglobulin was confirmed electrophoretically. The concentration of IgG was estimated by absorbance at 280 nm. The purified antibody was tested in radioimmunoassay for binding specificities (6, 7). Sterility of the antibody preparation was monitored by incubating a sample for 2 wk in thioglycolate broth and nutrient broth (Difco, Detroit, MI).

Prior to administration, the antibody preparation was centrifuged for 60 min at 100,000 × g to remove all immunoglobulin aggregates. Administration of Antibody. Twenty patients received a single 200- to 850-mg i.v. infusion of MAb 17-1A during the evaluation period (Table 1). In two patients, the infusions had to be discontinued prior to the completion because of urticaria. The antibody was diluted in 250 ml of normal saline and administered over at least 1 h in a Special Care Unit where trained personnel were present to manage potential toxic or allergic reactions. Patients were monitored for changes in pulse, blood pressure, and respiratory function during and after the infusion. Physical examinations were made after completion of the infusion and 1 day later to identify adverse reactions.

Human antimouse antibody response was assessed before and 1 wk after MAb infusion (4, 5). No patient with preexisting antibody against murine globulin was identified. Sera reactive after MAb administration...
were further assayed for the appearance of antidiotopic antibody weekly for 4 wk and then monthly for 3 mo (8). Patients were examined for signs and symptoms of serum sickness for 1 mo after the infusion.

RESULTS

Most patients tolerated the infusion well. Two patients developed urticaria, one of whom was treated with antihistamine. One patient developed nausea and another developed diarrhea in the immediate postinfusion period but these symptoms spontaneously resolved. There were no vasomotor changes, bronchospastic complaints, nor any delayed symptoms that could be associated with serum sickness. No hematological, hepatic, or renal changes were noted. Ten of 20 evaluable patients developed human anti-murine antibody. Eight of 10 patients showed anti-idiotype antibody responses, two patients did not raise such antibodies.

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Three of 20 patients had tumor effects which were documented and can be used to radioimage metastatic tumors (6, 7, 11, 12). Radiolocalization techniques can detect disease using monoclonal reagents not identifiable by conventional CAT scan evaluations (12).

The patient population in the present study differed considerably from that in the phase I study (4, 5). Patients in the present study had large tumor burden, a short expected survival time, and were required to cease all other therapies for a full month before entering the immunotherapy trial. Furthermore many patients in the first trial received single or multiple injections of MAb incubated with an autologous leukocyte preparation (4, 5), whereas patients in the present trial received MAb alone and in a single administration. Modification of any one of these parameters might alter the ultimate outcome of MAb therapy for the patient.

DISCUSSION

The murine MAb 17-1A has been an extremely valuable reagent for the study of human gastrointestinal adenocarcinoma (1-12). It binds to almost all colon adenocarcinoma cell lines tested and can be used to radioimage metastatic tumors (6, 7, 11, 12). Radiolocalization techniques can detect disease using monoclonal reagents not identifiable by conventional CAT scan evaluations (12).

The patient population in the present study differed considerably from that in the phase I study (4, 5). Patients in the present study had large tumor burden, a short expected survival time, and were required to cease all other therapies for a full month before entering the immunotherapy trial. Furthermore many patients in the first trial received single or multiple injections of MAb incubated with an autologous leukocyte preparation (4, 5), whereas patients in the present trial received MAb alone and in a single administration. Modification of any one of these parameters might alter the ultimate outcome of MAb therapy for the patient.

The heterogeneity of antigen expression in disseminated metastatic tumor, as demonstrated by the response of a patient’s hepatic metastasis but not by the abdominal wall metastasis, is of interest for future approaches to MAb immunotherapy but thus far has been observed in only 2 patients of our total series. Since other investigators (13) have demonstrated that antibody in cooperation with host effector cells can kill tumors of small size, it is impressive that some patients with larger tumor burden had also responded. As MAb 17-1A seems to exert its effect through armed macrophage mediators (3, 14), the minimal response in some of the patients may rest in the unfavorable ratios of these effector cells to billions of proliferating tumor cells. It is also worth stressing that the effector cell function in many patients showed partial regression and calcification, as documented by CAT scan, while the abdominal wall metastasis continued to grow. Because of the progression at the latter site, the patient was considered a nonresponder.

**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Site of primary</th>
<th>Site of metastasis</th>
<th>MAb dose (mg)</th>
<th>Carcinoembryonic antigen at time of antibody administration</th>
<th>Anti-mouse antibody</th>
<th>Anti-idiotype antibody</th>
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<td>Colon</td>
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<td>Colon</td>
<td>Lung</td>
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<td>Lung</td>
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<td>Colon</td>
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<td>200</td>
<td>33.8</td>
<td>-</td>
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</tbody>
</table>

* Response in liver metastasis but not in abdominal wall metastasis.

b Responders.
patients was impaired by previous treatments such as chemotherapy and radiation.

Of the group of patients described previously (8) and those included in the present study, seven had tumors that were altered in response to MAb treatment, and in 5 of these patients in the original study, antiidiotypic responses were demonstrated. Only one of the two responders with large tumor burden in the present study had detectable anti-idiotype antibodies.

These results support previous observations that a murine cytotoxic anticolorectal cancer MAb can modulate growth of adenocarcinoma in patients. Evidence continues to hold for variable responses in patients with large tumor burdens. Future studies in patients with small residual tumor burden are needed. Strategies that allow multiple exposures to MAbs reacting with different antigens on the cancer cells should allow more efficient treatment and overcome the problem of tumor cell heterogeneity.

ACKNOWLEDGMENTS

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REFERENCES

Fig. 1. CAT scan of pelvis in patient 32 taken before MAb administration delineates tumor area (arrow).

Fig. 2. CAT scan of pelvis at similar levels of the lesion (see Fig. 1) taken 4 mo after administration of 250 mg of MAb 17-1A. Note the marked reduction in the tumor area (arrow).
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