Phase I/II Study of G17-DT, an Anti-Gastrin Immunogen, in Advanced Colorectal Cancer

Andrew M. Smith, Timothy Justin, Dor Michaeli, and Susan A. Watson

Academic Unit of Cancer Studies, University of Nottingham, Nottingham NG7 2UH, United Kingdom [A. M. S., T. J., S. A. W.], and Aphton Corporation, Woodlands, California 95776 [D. M.]

ABSTRACT

Gastrin is a growth factor for colorectal cancer, and therefore, anti-gastrin hormone therapy has a potential role in treatment of this disease. The gastrin immunogen gastrin-17-diphtheria toxoid (G17-DT; Gastrimmune) produces anti-G17 antibodies that have been shown to be effective in the treatment of colorectal carcinoma in preclinical models. Fifty patients with advanced colorectal cancer were treated with G17-DT in a multicenter, sequential group, open label Phase I/II study. Primary injections with two booster doses were given by i.m. injection. The main aim of the study was to assess the safety and efficacy of the production of anti-gastrin antibodies. Locally developed and standard WHO toxicity measurements with RIA and Scatchard analysis for antibody assessment were used. One center measured tumor response radiologically. Eighty% of patients produced a measurable antibody response. Antibodies of high affinity (median $K_d = 0.295 \text{nM}$; interquartile range, 0.16–0.41 nM) were detected between 4 and 12 weeks after primary injection. The antigen binding capacity was high at $2.8 \times 10^{-9} \text{M}$ (interquartile range, $5.1 \times 10^{-10}$ to $7.25 \times 10^{-9} \text{M}$). The treatment was well tolerated with no systemic side effects seen. Myalgia at the injection site was seen in 46% of patients with severe pain caused by the formation of a sterile abscess seen in 14% of patients. The abscesses were all drained under ultrasound guidance, and the patients recovered fully within 6 weeks. No radiological responses were seen, but two patients had stable disease. G17-DT immunization produces anti-G17 antibodies in patients with advanced colorectal cancer. The antibodies were of an affinity high enough to compete with the cholecystokinin B/gastrin receptor for G17 binding with adequate capacity to neutralize postprandial gastrin surges. Additional dose-ranging studies have been performed in patients with gastric cancer using 100- and 200-$\mu$g doses of G17-DT formulated without adjuvant and the emulsifier aluminum monostearate. In addition, the effect of immunizing at different time intervals has been determined.

INTRODUCTION

Colorectal cancer is the second most common cause of cancer deaths in the United Kingdom, accounting for ~16,000 deaths/year. Despite advances in surgery, chemotherapy, and radiotherapy, only modest improvements in overall mortality have been achieved in the past 30 years. Cancer vaccines offer a new potential treatment option.

Gastrin is a peptide hormone that is important in the regulation of acid secretion and the growth of both normal and malignant gastrointestinal epithelium (1), and it exists in two amidated forms composed of 17 and 34 amino acids, denoted G17 and G34, respectively. Colorectal tumor cell lines and human cancers may express a number of isoforms of the gastrin/CCKB receptors (2–8) and produce their own gastrin (9–13). Therefore, the tumor cells can potentially respond to circulating endocrine gastrin (14–17) and the locally produced gastrin, which acts in an autocrine or paracrine manner (18, 19). The tumor-associated gastrin is composed mainly of precursor forms, particularly glycine-extended G17, which have also been demonstrated to have a proliferative effect (20, 21).

Elevation of the circulating gastrin level has been shown in animal models and humans to enhance the proliferation of the normal colonic mucosa (20–23). As a result, there is an increase in incidence of colorectal cancer in hypergastrinemic patients (24). In addition, studies in the APCMin model of polyposis coli have shown hypergastrinemia induced by omeprazole administration and after infection with Helicobacter pylori promotes the proliferation and progression of colorectal adenomas (25). Effective inhibition of gastrin may, therefore, be beneficial as a therapy in colorectal cancer, potentially in prevention, beneficial as an adjuvant, or even beneficial in advanced disease.

Gastrin/CCKB receptor antagonists have been assessed in patients with gastrointestinal tumors. The antagonists appeared to be ineffectual (26, 27), and it was initially assumed to be because of their lack of potency, with relatively high concentrations required to displace amidated G17 (28, 29). The results of studies assessing tumor receptor profiles indicate that the lack of efficacy is probably also a result of the fact that several receptor subtypes mediate the action of gastrin (2, 8).

A potential method to circumvent the problem created by the presence of numerous gastrin/CCKB receptor isoforms is to...
neutralize gastrin before it interacts with its receptor. Gastrim-
nume, an anti-gastrin immunogen, produces in situ neutralizing
antibodies directed against the forms of gastrin that have a
proliferative action before they interact with the receptor.

Gastrimmune is an immunoconjugate consisting of the nine
NH2-terminal amino acids of human G17 linked via a peptide
spacer to DT. DT acts as the immunogenic carrier, and the G17
sequence acts as a B-cell epitope. The peptide spacer allows
the gastrin moiety to be orientated spatially in such a way that B
cells recognize the whole sequence and thus raise high affinity,
neutralizing antibodies (30, 31).

Because the immunogen is composed of the NH2-terminal
amino acids, the raised antibodies neutralize both amidated G17
glycine-extended G17. In an animal model, after priming
injections, antibody titers were raised that were higher than
those required to neutralize all serum G17, and thus excess
unbound antibody was available for neutralization of tumor-
associated gastrin molecules (32).

By using active immunization with species-specific
Gastrimmune in a pig model, immunoneutralization of G17
was shown to inhibit acid secretion without having any antiprolif-
erative effects on the gastrointestinal mucosa, indicating that
normal trophic effects of other gastrin species, such as G34, are
preserved (33). Antibodies raised by Gastrimmune have been
evaluated in a number of colorectal tumor models and have been
shown to exert strong therapeutic effects in primary tumors (34)
and in both hepatic and lung metastasis models (35, 36).

After it was demonstrated that Gastrimmune has an anti-
tumor effect in animal models, a Phase I/II study was performed
in patients with advanced colorectal cancer. The primary aim
of this study was to assess the safety and efficacy, in terms of
antibody response, of Gastrimmune in patients with colorectal
adenocarcinoma. Secondary aims were to assess the effect of
formulation (the dose of Gastrimmune; the addition of an adju-
vant in the priming dose, nor-MDP, with the emulsifier
AMS. The third formulation was a simple water-in-oil emulsion
without adjuvant or emulsifier).

Gastrimmune was administered as an i.m. injection. The
primary injection and subsequent boosters were given at differ-
ent sites. The first immunization was injected into the left thigh,
the second immunization was injected into the right thigh, and
the third immunization was injected into the left buttock. Each
dose of Gastrimmune was drawn up into a syringe immediately
before administration to minimize contact with plastic and pos-
sible adsorption of the peptide conjugate.

**Drug Dosage and Treatment Schedule.** Each patient
was to receive three injections of Gastrimmune. After a 1-week
assessment period, a primary injection was to be given, followed
by two additional immunizations spaced 4 weeks apart. The
dose level for each group of six patients was to escalate from
three injections of 10 μg of immunogen for the first group, to
100 μg for the second group, to 250 μg for the third group. The
fourth group was to receive 10 μg of immunogen with 3 μg of
nor-MDP adjuvant in the first injection only, and the fifth group
was to receive 100 μg of immunogen with 3 μg of nor-MDP
adjuvant in the first injection only. An unadjuvanted formulation
without the emulsifier AMS was then administered in an esca-
lating dose, from 165 μg to the sixth group, 330 μg to the
seventh group, 495 μg to the eighth group, and 990 μg to the
ninth group (Table 1).

**Patient Monitoring.** The patients were seen in specially
designated clinics. Before the treatment commenced, histories
and physical examinations were performed, and the following
evaluations were obtained: (a) Karnofsky score; (b) full blood
count; (c) urea and electrolytes; (d) liver function tests; (e) 24-h
creatinine clearance; (f) CEA; (g) immunoglobulins and autoan-
tibodies; (h) fasting G17 and anti-gastrin antibody; (i) chest
radiograph; and (k) CT scan (Nottingham patients only).

After each immunization, the patient was given a daily
diary to assess local tolerance of the injection and interference
with the activities of daily life. The patient was required to
record the pain at the injection site and how the discomfort from
the injection interfered with the patient’s normal daily activities
on an ordinal scale from 0 to 10. The diaries were checked at
each visit. The investigator recorded an assessment of the degree
of discomfort from the injection site and the degree of functional
impairment attributable to the injection site that the patient

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**PATIENTS AND METHODS**

**Methods.** The trial was designed as a multicenter, se-
quential group, open label study. It was planned that 54 patients
with advanced colorectal cancer would be admitted to the study
in sequential blocks of six. The first patient entered in June

**Patient Selection.** Patients, ages 18 years or older, with
histologically verified adenocarcinoma of the colon or rectum
that was either locally advanced, inoperable, recurrent, or met-
astatic and that was not amenable to curative surgery and/or
radiotherapy, were candidates for this study. Other eligibility
criteria included: (a) life expectancy >3 months; (b) Karnofsky
index ≧50%; (c) no other neoplasms apart from colorectal
cancer (except treated basal cell carcinoma of the skin or cancer of
the uterine cervix, stages 0–1); (d) no acute intercurrent
illness; (e) no patients considered to be a poor medical risk
because of nonmalignant systemic disease or grossly abnormal
laboratory results; (f) no patients who had received any other
anticancer therapy within 3 weeks; (g) no patients immunologi-
ically compromised, including those on systemic corticosteroid
therapy; (h) no women of childbearing age; (i) no positive
immediate hypersensitivity reaction to skin testing with Gastrimmune; and (j) adequate hemopoiesis (hemoglobin >10
g/dl; WBC count >4.0 × 109/liter; platelets >100 × 109/liter). Written informed consent was obtained according to institu-
tional guidelines.

**Gastrimmune Formulation and Administration.**
Gastrimmune was supplied by Apton Corporation (Wood-
lands, CA). Gastrimmune is a sterile, milky white, semisemous
water-in-oil emulsion. The G17 immunogen was dissolved in a
PBS aqueous phase that was mixed with a surfactant and oil
phase to form a water-in-oil emulsion. Three formulations of
Gastrimmune were used to determine whether they would affect
local tolerance and antibody production. The basic formulation
included an emulsifier, AMS. The second formulation contained
an adjuvant in the priming dose, nor-MDP, with the emulsifier
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Table 1  The G17-DT dose groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Immunogen schedule (μg)</th>
<th>Immunogen (μg)</th>
<th>Adjuvant (μg)</th>
<th>Emulsifier AMS</th>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<tr>
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<td>Present</td>
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<td>4</td>
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<td>Absent</td>
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<tr>
<td>6</td>
<td>165</td>
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<tr>
<td>9</td>
<td>990</td>
<td>0</td>
<td>Absent</td>
<td>0.3</td>
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</tr>
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</table>

Table 2  Volumes of individual components used in the
radioimmunoassay of anti-G17 antibodies

<table>
<thead>
<tr>
<th>Volume (μl)</th>
<th>Dilution</th>
<th>125I-G17</th>
<th>Sera dilution</th>
<th>Stripped sera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backgrounda</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Total CPM</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Test sera</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Positive serum</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

*Radioactivity associated with tube assayed directly.

Patients’ sera were diluted in Veronal buffer initially at a
1:10 dilution and in a 3-fold dilution series thereafter. A positive
control antiserum (Rabbit antihuman Gastrimmune) was also
prepared in buffer at the same dilutions.

Sera dilutions were then aliquoted into glass tubes that had
been coated previously with 2.5% polyethylene glycol (Mw
10,000; Sigma, Poole Dorset, United Kingdom). Stripped sera
were added to the control tubes. This was prepared from pooled
human serum that was added to charcoal that had been previ-
ously soaked overnight in 100 ml of 0.02 M Veronal buffer. This
was mixed and incubated at 4°C for 30 min, after which it was
centrifuged at 3000 × g for 10 min. The supernatant was
collected and passed through a C18 Sep-pak filter that had been
washed previously with 2.5% polyethylene glycol (10 ml of 50% acetonitrile [diluted in
0.02 M PBS (pH 7.2)]) and 20 ml of 0.02 M Veronal buffer. After
passage through the Sep-pak filter, the serum was collected,
filtered through a 0.20 μm Millipore filter, and stored frozen at
–20°C until use. The following tubes were set up as described in
Table 2.

The tubes described in Table 2 were incubated for 72 h at
4°C (all tubes were prepared in triplicate). After the incubation,
100 μl of newborn calf serum (Sigma) and 250 μl of 25% polyethylene glycol (Mw 8000; Sigma) were added to each tube,
which were then vortexed. The tubes were then centrifuged at
3000 × g for 30 min at 4°C. The supernatant was aspirated, and
the pellet from each tube was counted on a gamma counter (83%
counting efficiency). The mean of each triplicate was used, and
each result was calculated as the percentage of 125I-labeled G17
bound using the following equation:

\[
\% \text{G17 bound} = \frac{\text{Test cpm} - \text{background cpm}}{\text{Total cpm/tube} - \text{background cpm}} \times 100
\]

Titer was evaluated from the titration curve.

RESULTS

Fifty patients entered into the study. Thirty-three (66%) of
the patients were male, and 17 (34%) were female. The mean
age at entry was 65.1 years, with a minimum age of 40 and a
maximum age of 84. Karnofsky scores ranged from 60 to 100%,
with a mean of 84% and a median of 100%. Mean weight was
66.3 kg, with a minimum weight of 41 kg and a maximum
weight of 106 kg.

Six patients died during the study from advanced disease.
Thirty-four patients received all three immunizations, 15 pa-
tients received two injections, and 1 patient received only a

experienced during the period since their last injection. In ad-
dition, the investigator inspected the injection site.

The patient was seen at 2-week intervals for 12 weeks;
these visits included history and examination, full blood count,
urea and electrolytes, liver function tests, CEA, and anti-gastrin
antibodies. At 12 weeks, all of the investigations that were
performed at the beginning of the study were repeated. Further
follow-up was arranged at 8-week intervals. This allowed the
patient to air any problems and gave the investigator an oppor-
tunity to evaluate long-term antibody response.

This was performed pretreatment and posttreatment. The
degree and site of disease was recorded. If possible, three to four
marker lesions were measured at both times. All of the CT scans
were interpreted by a single consultant radiologist. Standard
WHO criteria for objective response assessment were used.
Partial response was defined as a >50% reduction in the sum of
the products of the largest perpendicular diameters of all meas-
urable disease sites. Progressive disease was indicated by a
>25% increase in the size of at least one measurable lesion or
the appearance of a new lesion. Stable disease was defined as an
increase in disease measurements of <25% or a decrease of
<50%.

Anti-Gastrin Antibody Assay. Serum was obtained by
centrifugation at 4°C after the formation of a clot and stored at
−70°C until analysis. 125I-labeled G17 (New England Nuclear-
DuPont; specific activity, 2200 mCi/mmol) was reconstituted in
distilled water to a concentration of 300 Ci/ml. The radiolabeled
G17 was diluted in Veronal buffer [0.02 M (pH 8.4)].

**Table 1** The G17-DT dose groups

The table shows the variation in composition of the immunogen
between groups.

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**Table 2** Volumes of individual components used in the
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*Radioactivity associated with tube assayed directly.
single immunization. Failure to complete a course of immunizations was because of either advancing disease (7 patients) or as a result of a reaction at the local injection site (9 patients).

**Assessment of Safety**

**Systemic Effects.** The immunogen was well tolerated. Only two patients complained of nausea and vomiting that were potentially related to treatment. No other systemic symptoms were noted. Apart from hematological changes that would be expected from advancing colorectal cancer, there were no significant changes in the blood tests throughout the study. There was no effect on renal function, as measured by serial urea and electrolytes and by pretreatment and posttreatment 24-h creatinine clearance. Importantly, there was no change in immunoglobulin levels and no development of autoantibodies (parietal cells, smooth muscle, thyroid, intrinsic factor, reticulin, antinuclear and mitochondrial antibodies, and rheumatoid factor) after administration of G17-DT.

**Local Tolerance.** Twenty-four patients (46%) experienced a mild myalgia at the injection site after at least one of the injections. In most cases, the patient experienced mild discomfort that lasted between 2 and 5 days and did not interfere with any activities of daily life. The mean pain score for all groups was 0.54 (maximum, 10). There was no significant difference in the pain scores among the groups or the formulations (Table 3). The onset of the myalgia was variable and did not occur more frequently after a particular immunization. When patients experienced injection site pain, no abnormality could be found on examination in most cases.

However, a group of seven patients (14%) developed sterile abscesses at an immunization site. Before the detection of the abscess, there was severe pain and limitation of movement of the affected limb in every patient. The diagnosis was made after drainage, the pus cells; however, no growth was seen on the culture, and a diagnosis of a sterile abscess was made. After drainage, the patients made a complete recovery, which took up to 6 weeks.

After the development of abscesses in the group receiving adjuvant, no additional patients were recruited to the adjuvant formulation groups. The abscesses in group 8 (495 µg) did not occur until relatively late in the study, and four patients had been recruited to group 9 (990 µg). No additional patients were entered into the study.

**Assessment of Efficacy**

**Anti-Gastrin Antibody Response.** Using the criteria that 10% of 125I-labeled G17 binding was the threshold for a measurable response, 40 of the 50 patients produced antibodies after immunization with Gastrimmune. The response rate varied among the groups, as seen in Table 4. The lowest response rate was seen in group 1 (10 µg).

All patients achieved a ≥10% 125I-labeled G17 binding between weeks 4 and 12. Differences in the formulation of Gastrimmune did not alter the time to antibody formation.

At week 12, the \( K_d \) was 0.295 nM (interquartile range, 0.16–0.41 nM). The median antigen binding capacity of the antibodies was \( 2.8 \times 10^{-9} \) mol/liter (interquartile range, \( 5.1 \times 10^{-10} \) to \( 7.25 \times 10^{-9} \) M). There was no significant difference in the characteristics of the antibodies produced by different dose groups. Several patients have been followed-up after the completion of the study. Antibody titers are maintained, up to a maximum of 2 years.

We have been able to measure the presence of excess anti-G17 antibodies and excess amounts of bound G17. However, measurement of free G17 in the presence of antibodies and gastrin/antibody complexes is technically difficult. Initially, several serum manipulations are required to try to separate the free gastrin fraction, which appears to be small. The numerous

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**Table 3** Number of immunizations received and the pain scores of each group

<table>
<thead>
<tr>
<th>Dose (µg) emulsion</th>
<th>10</th>
<th>100</th>
<th>250</th>
<th>10 + 3</th>
<th>100 + 3</th>
<th>165</th>
<th>330</th>
<th>495</th>
<th>990</th>
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<td>Volume (ml)</td>
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<td>0.25</td>
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<td>Group</td>
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<tr>
<td>Maximum mean pain score</td>
<td>0.01</td>
<td>0.03</td>
<td>0.61</td>
<td>0.08</td>
<td>0.33</td>
<td>1.07</td>
<td>0.58</td>
<td>2.08</td>
<td>0.8</td>
</tr>
<tr>
<td>Maximum mean interference with daily activities score</td>
<td>0.10</td>
<td>0.01</td>
<td>0.60</td>
<td>0.01</td>
<td>0.48</td>
<td>0.96</td>
<td>0.52</td>
<td>1.39</td>
<td>0.54</td>
</tr>
<tr>
<td>No. abscesses/fluid collections</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

* Pain score: 0, no pain; 10, worst pain. Interference score: 0, no interference; 10, completely inactive or bedbound.

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**Table 4** Positive antibody responders by group

<table>
<thead>
<tr>
<th>Dose</th>
<th>Gastrimmune (µg)</th>
<th>Adjuvant (µg)</th>
<th>Responder % responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>2/6</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>5/6</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>250</td>
<td>5/6</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>Yes</td>
<td>3/4</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>Yes</td>
<td>5/6</td>
</tr>
<tr>
<td>6</td>
<td>165</td>
<td>5/6</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>330</td>
<td>6/6</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>495</td>
<td>5/6</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>990</td>
<td>4/4</td>
<td>100</td>
</tr>
</tbody>
</table>
manipulations result in an assay that is not reproducible. Advice was sought from Professor John Walsh, who believes that measurement of the free fraction in vitro is technically difficult at this time. He suggested that an in vivo bioassay would be more effective. This has been performed in a rat gastric fistula model. The induction of anti-gastrin antibodies resulted in significant inhibition of G17-stimulated acid output. This bioassay confirms the effectiveness of the antibodies to bind G17 (25).

**Disease Response.** Although this was a Phase I/II study, response data were collected. Four patients had lung metastases evident on their original screening chest radiograph. These had all progressed by the time of the poststudy examination. Two patients developed lung metastases during the study period.

Metastatic burden was assessed by a CT scan. Sixteen patients had pretreatment CT scans, and 14 patients had the investigation repeated at the end of the study. There were no complete or partial responses, with 12 of 14 patients having progressive disease reflected in elevated CEA levels. Two patients had stable disease, both having had progressive disease before study entry. One patient had a local rectal recurrence; the other patient had liver metastases (data not shown).

Overall, the CEA levels rose during treatment in all study groups. However, in five patients the CEA remained stable, and one patient showed a modest reduction (data not shown).

**DISCUSSION**

The principal aims of this study were to determine the safety and efficacy of the immunogen in terms of an antibody response. Gastrimmune immunization was well tolerated systemically. Only two patients associated nausea and vomiting with immunization. Importantly, immunization did not induce autoantibody production.

Half of the patients had mild myalgia after immunization. This was short-lived and did not interfere with their daily life activities. Abscess formations occurred in a group of patients but were easily treatable, and symptoms were resolved within a short period of time. Initially, it was thought that the adjuvant nor-MDP was responsible for abscess formation; however, abscesses occurred in the formulation without adjuvant or emulsifier. There were no discernible factors that predisposed patients to abscess formation. There was also no pattern or timing to abscess formation. We are unable to explain why the majority of patients tolerate the immunogen well and others develop abscesses. However, unadjuvanted immunogen <330 μg did not result in abscess formation.

Excess antibody titers were seen in 40 of 50 (80%) patients with advanced colorectal cancer; this is despite only 36 of 50 patients having a complete immunization course. The $K_D$ of the antibodies was such that they would be able to compete for gastrin binding with CCKB receptors expressed by colorectal cancer cells, the affinities of which range from 0.1 to 0.5 nM (37, 38). The median antigen binding capacity was such that it would be able to absorb a gastrin concentration ~47 times greater than that seen postprandially (1). Although not a primary aim of the study, assessment of the efficacy of antibodies raised by Gastrimmune indicated that there was no tumor regression, and stable disease was seen in only 2 of 14 patients evaluated. It is likely that gastrin neutralization may slow growth by the removal of a major proliferative factor, and a slowing of tumor growth would not be measurable by methods used in the present study. We believe that G17-DT may have a role as an adjuvant in colorectal, gastric, and pancreatic cancer. In addition, gastrin appears to be an important growth factor early in the development of colorectal cancer; it appears to be controlled, in part, by the APC gene. G17-DT, therefore, may have a role in the prevention of colorectal cancer in high risk cases.

The most effective method of evaluating the potential cytostatic effect of G17-DT is a survival study. Such studies are currently underway in both gastric and pancreatic adenocarcinomas. These tumors have been chosen because gastrin also has a proliferative effect in these cancers, and there is a paucity of adjuvant therapies that are beneficial. In gastric cancer, G17-DT will be assessed in a prospective, placebo-controlled trial with patients who have had a potentially curative resection for stage II/III cancer. Pancreatic cancer patients will be randomized to receive either G17-DT or gemcitabine.

**REFERENCES**

Phase I/II Study of G17-DT, an Anti-Gastrin Immunogen, in Advanced Colorectal Cancer

Andrew M. Smith, Timothy Justin, Dor Michaeli, et al.


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