Ovarian Cancer *BRCA1* Gene Therapy: Phase I and II Trial Differences in Immune Response and Vector Stability

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ABSTRACT

Gene therapy with viral vectors has shown some promise in nude mice models and in initial Phase I trials of patients with extensive metastatic cancer. A Phase I clinical trial (D. L. Tait et al., Clin. Cancer Res., 3: 1959–1968, 1997) of ovarian cancer patients treated with i.p. retroviral LXSN-*BRCA1*sv gene therapy reported stable vector, minimal antibody response, and tumor reduction. We initiated a Phase II trial on patients with less extensive disease to evaluate vector pharmacokinetics, immune response, toxicity, and efficacy. Patients received a surgically implanted peritoneal catheter to administer infusions of vector, as well as to retrieve daily samples of peritoneal fluid for analysis. Ovarian cancer patients received four daily i.p. injections of LXSN-BRCA1sv vector therapy for three cycles, 4 weeks apart. Patient peritoneal fluid and plasma were analyzed extensively by PCR, Western blot, complement level (CH50), and chemical and hematological tests. Phase II patients showed no response, no disease stabilization, and little or no vector stability. Because of vector instability and rapid antibody development, which differed dramatically from the Phase I trial data, the trial was terminated after treatment of six patients. Immune system status appears to have played a major role in whether gene therapy was effective. Comparison of Phase I and II patients showed significant differences in tumor burden, immune system status, and response to *BRCA1* gene therapy.

INTRODUCTION

Phase I studies with retroviral vectors expressing HSV-TK, p53, and BRCA1 have reported tumor reduction in some patients with advanced cancer (1–3), suggesting that gene therapy may ultimately benefit cancer patients. Cancer gene therapy approaches include a number of strategies: immune modulation, altering expression of drug resistance genes, inhibition of dominant oncogenes, and overexpression of tumor suppressor genes (3).

The overexpression of tumor suppressor genes is a genetic strategy for cancer gene therapy and includes gene transfer protocols involving vectors expressing p53 and BRCA1. Although the molecular function of BRCA1 is controversial and may include DNA repair or transcriptional functions (4), overexpression of BRCA1 into sporadic breast or ovarian cancer cells that usually show low BRCA1 expression (5, 6) results in growth inhibition and tumor suppression (2, 5, 7, 8). Growth inhibition by BRCA1 has itself been controversial, leading some to question the rationale for *BRCA1* gene therapy (9), but subsequent studies have shown growth inhibition or tumor suppression by *BRCA1 in vitro* (2, 4, 8–15) or *in vivo* (2, 7, 8, 11). The mechanism of growth inhibition by BRCA1 is unknown and may involve interactions with p21 (10) or p53 (11) or induction of apoptosis (12). Our prior Phase I study of 12 patients with extensive ovarian cancer treated with a retroviral vector expressing the BRCA1 splice variant LXSN-BRCA1sv demonstrated vector stability, minimal immune response, gene transfer and expression, and tumor reduction in some patients (2).

Because initial Phase I gene therapy trials have necessarily been focused on treatment of patients with extensive metastatic disease, few or no data are available regarding vector stability or immune response in patients with less extensive disease. This is an important gap in our current understanding of patient responses to vector gene therapy, because patients with localized small-volume disease may represent the best target population for present-generation viral vectors.

MATERIALS AND METHODS

Protocol Approval. The protocol was approved by the Institutional Biosafety Committee, Clinical Protocol Review and Monitoring Committee, Committee for the Protection of Human Subjects, and the Clinical Research Center protocol review committee of Vanderbilt University. The protocol was also exempted by the Recombinant DNA Advisory Committee to the NIH and was approved by the United States Food and Drug Administration (FDA).

Retroviral Vector Production, Administration, and Characterization. The structure and sequence of the retroviral vector are as reported previously in the Phase I trial (2). The LXSN-BRCA1sv retroviral vector used incorporates a BRCA1 splice variant (GenBank accession no. AF005068) originally.
used to demonstrate growth inhibition and tumor suppression (7, 8). Vector structure, production, and testing were as previously described (2). Briefly, PA317 producer cells were grown in a Corning Costar Cell Cube System (Corning Incorporated, Acton, MA) perfused with Aim V (serum-free medium approved by the FDA for injection into patients; Life Technologies, Inc., Gaithersburg, MD), and LXS-N-BRCA1sv retrovirus-containing supernatant was collected steriley under optimal cGMP conditions. Polybrene (Sigma Chemical Co., St. Louis, MO) was added to 8 μg/ml final concentration before aliquots were frozen at −70°C. Extensive cGMP testing was done on aliquots of vector taken before, during, and after production, and the vector was found to be negative for endotoxin, bacterial, mycoplasma, and viral contamination; and replication-competent retroviruses (by PG4 assay after amplification on Mus musculus). Aliquots of vector were thawed and transported to the patient on wet ice. Infusions of vector were always initiated within 1 h of thawing the vector aliquot. Either 100 ml (patients 1–3) or 33 ml (patients 4–6) of vector were administered with 1.5 liters of saline i.p. daily for 4 days. The patients received three courses of treatment in 3 months before second-look laparoscopy was performed.

The biological activity of the vector lot used in the Phase II trial was characterized using the lot-release criteria established with the FDA and compared with the biological efficacy of the vector used in the Phase I trial. The Phase II vector lot was shown to produce a titer transforming G418 resistance to NIH 3T3 fibroblasts, which was directly comparable with that of the Phase I vector lot. It also showed greater than 90% reduction of colony formation of MCF-7 cells, thereby demonstrating similar growth inhibition in vitro as recorded for the Phase I lot. Most importantly, both Phase I and Phase II vector lots were used in animal tumor suppression studies and showed an identical reduction in tumor volume and increased survival in both ovarian cancer and breast cancer models (data not shown; data on file with the FDA).

**Patient Selection and Eligibility Criteria.** Patients with recurrent or persistent epithelial ovarian cancer were considered for study. All patients had to have been treated previously with standard debulking surgery and platinum/paclitaxel first-line chemotherapy. Written informed consent was obtained from all patients before investigations to determine eligibility were performed. Inclusion criteria for the Phase II study included minimal recurrent or persistent epithelial ovarian cancer with no tumor dimension greater than 3 cm confined to the peritoneal cavity; age ≥18 and <75 years; Gynecologic Oncology Group performance status ≤2; life expectancy >3 months; 4-week interval since previous surgery and/or cancer therapy; and adequate hematological (WBC count >4000/μl), hepatic (bilirubin <2 mg/dl; aspartate aminotransferase <2 × normal level), and renal (creatinine <1.5 mg/dl) functions. Exclusion criteria included active bacterial infections; other concomitant cancer therapies; heart failure (New York Heart Association class 4); respiratory, renal, hepatic, or hematological dysfunction; and anticoagulant or antiplatelet therapy. Stages at diagnosis were III (five patients) and IV (one patient). Mean number of previous chemotherapy regimes was two, compared with more than three for the Phase I trial (Table 1).

**Study Design.** Patients considered eligible for the study underwent diagnostic laparoscopy or laparotomy to assess and confirm minimal i.p. disease. A peritoneal Port-a-Cath (Simms Deltec, St. Paul, MN) was placed for access to the peritoneal cavity. Patients were admitted to the Clinical Research Center at Vanderbilt University for 4 consecutive days of i.p. LXS-N-BRCA1sv gene therapy. The starting dose was $3.3 \times 10^9$ viral particles per day, but this was reduced for three patients to $1.1 \times 10^9$. Objective end points to assess toxicity included daily peritoneal and blood samples to evaluate cell counts, serum chemistries, bacterial cultures as indicated, and vector stability; viral uptake by cells; and the presence of antibodies to vector envelope proteins. Initial measurable tumor was determined surgically or by computed tomography. Patients were treated at 4-week intervals. At the completion of cycle 3 of therapy, computed tomography was again performed to assess disease stabilization or progression. Patients were removed from the study if tumor progression was detected. At the completion of six cycles of therapy, patients would undergo surgical re-examination by laparoscopy to document disease status. Of the six preliminary patients enrolled on the study, five completed three cycles of therapy and were then removed secondary to radiographic progression of disease. One patient was removed after 2 cycles on development of pulmonary metastasis.

**Vector Stability and Immune Studies.** Presence of retroviral vector recoverable from patient fluids was determined by PCR as previously described (2). Briefly, samples of patient fluids (blood and peritoneal fluid) were taken before the first infusion of vector and immediately before subsequent infusions. This gave an approximately 24-h survival test of the vector in vivo. Peritoneal fluid was centrifuged and separated into a fluid sample and a cell pellet sample. Leukocytes and plasma were isolated from the blood sample. PCR was then done on all samples with primers used in the prior Phase I study as described (2). Because PCR fluid determinations were performed on 5 μl of peritoneal supernatant and PCR cell pellet determinations were performed on cells from as much as 10 ml of peritoneal fluid, the PCR cell pellet assay had greater sensitivity (i.e., it could detect smaller quantities of vector). Patient plasma and peritoneal fluids were frozen and then used for measurements of CH50 or Western blotting for envelope antibodies. CH50 was performed following the manufacturer’s instructions on plasma and peritoneal samples, using antibody-sensitized sheep erythrocytes (Sigma Chemical Co.). Basically, patient peritoneal fluid or plasma was incubated with antibody-sensitized sheep erythrocytes in sodium barbital buffer for 30 min at 37°C. The extent of antibody-dependent lysis was then determined by pelleting unlysed red cells and measuring hemolysis in the supernatant by spectrophotometry against a standard curve. Standard complement serum (Sigma Chemical Co.) was used as a control standard. Western blotting for envelope antibodies was performed by electrophoresis of purified retroviral particles derived from murine leukemia virus-Moloney Spleen (Quality Biotech, Inc., Camden, NJ) on SDS-PAGE gels followed by electrotransfer to nylon membranes and then incubation of nylon membranes with patient antibodies at dilutions (titers) between 22 and 740. Antibodies were visualized by incubation with a 1:10,000 dilution of peroxidase-conjugated secondary antibody directed against IgG heavy and light chains (Pierce Chemical Co., Rockford, IL). Positive controls for the Western
blots included primary antibodies directed against Mr 70,000
and 30,000 envelope proteins (Quality Biotech, Inc.).

Neutralizing antibodies were detected by incubating 50 μl
of patient plasma or peritoneal fluid with LXSN-BRCA1sv
retroviral vector for 60 min and then adding this to NIH3T3
target cells for 1 h in the presence of 8 μg/ml Polybrene. The
following day, 1 mg/ml G418 was added to the medium, and
colony counts were performed 7 days later. Control plasma or
peritoneal fluid did not decrease the titer of G418 resistance, and
pretreatment samples of Phase I and Phase II patients did not
neutralize virus in this assay (neutralization was defined as a
greater than 80% reduction of G418-resistant colonies).

Statistical Analysis. The primary goal of this Phase II
clinical trial was to estimate the overall response rate (complete
and partial recovery) of BRCA1 gene therapy in patients with
ovarian cancer. Thirty to 40 patients would be enrolled in the
study. A two-stage accrual design described by Simon (16)
would ensure that the number of patients exposed to this therapy
was minimized. With evidence that the true underlying overall
response rate is at least 20%, consideration would be given for
further testing of this trial. However, if BRCA1 gene therapy is
inactive in patients, the study should be terminated early. Ini-
tially, 15 eligible patients were planned to be entered into the
study. If there was no response in these 15 patients, the trial
would be terminated with the conclusion that there was little
evidence to suggest that the overall response rate would reach
20%. Although six patients without a clinical response did not
satisfy this early stopping rule, the complete lack of vector
stability and marked difference in immune response compared
with the Phase I trial led us to stop the trial after consultation
with the FDA.

RESULTS

Because the gene transduction rate of the LXSN-BRCA1sv
retroviral vector was significantly higher in smaller tumors than
in the center of larger tumors, we wished to determine whether
BRCA1 vector gene therapy would be more effective in patients
who had tumors less than 2 cm in diameter. To answer this
question, we initiated a Phase II trial in patients with smaller-
volume ovarian cancer that was designed to evaluate vector
stability, immune response, efficiency of gene transfer, and
extent of tumor reduction in these patients.

Patients received four daily doses of gene therapy with
saline (i.p.) monthly for 3 months before second-look laparos-
copy and photography. If disease stability or regression were
observed, then the patient would be treated for another 3
months. Six female patients, median age 49 years (range, 39–
67; Table 1) with epithelial ovarian carcinoma were entered into
the Phase II study and treated with i.p. injection of the retroviral
vector LXSN-BRCA1sv, a splice variant of BRCA1 (7, 8). The
extent of disease of patients was quantitated by laparoscopy and
photography (Fig. 1a) and thus differed greatly from the exten-
sive disease found in the Phase I patients (Fig. 1b). All Phase II
patients had tumor nodules smaller than 3 cm in diameter. These
eligibility criteria were created in consultation with the FDA and
were based on observations in the Phase I trial, which indicated
that retroviral vector treatment was ineffective against large
bulky tumors and more effective in reduction of small, miliary

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<th>Table 1</th>
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<td>Phase II mean</td>
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<td>Phase I mean</td>
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P(I versus II) = 0.022

Prior number of chemotherapy cycles.

Phase II and II Retroviral BRCA1 Gene Therapy

on October 2, 2017. © 1999 American Association for Cancer Research.
tumors less than 2 cm in diameter (2). Patients 1–3 were treated with $3.3 \times 10^9$ viral particles per day, and patients 4–6 had their dose reduced to $1.1 \times 10^9$ viral particles per day after we consulted with the FDA because of development of anti-retroviral vector antibodies. Nutritional status and immunocompetence were evaluated with serum albumin levels and complete blood counts. The mean albumin level was 3.92 g/dl compared with 3.24 g/dl in Phase I patients ($P = 0.003$, paired t test). Total WBC counts were statistically different between Phase II and Phase I patients, but no difference was noted in hematocrits or absolute lymphocyte counts (Table 1). Graphing WBC counts versus albumin illustrates the marked distinction between the immunoresponsive, relatively healthy Phase II patients and the Phase I patients (Fig. 1c).

PCR analysis with the vector-specific primers used in the Phase I studies to detect retroviral vector (2) was used to monitor vector stability and detect the presence of vector DNA in transduced peritoneal cells. This PCR assay did not detect vector in Phase II pretreatment samples of peritoneal fluid or pretreatment cell samples or biopsies (Table 2). Multiple PCR analyses on plasma samples showed no detectable vector in plasma; PCR samples were positive in the lymphocyte fraction in 5 of 65 PCR samples, which may represent lymphocyte trafficking from peritoneum or circulating tumor cells. Twenty-four h after each infusion (just before the next dose), we sampled peritoneal fluid to assess stability and uptake of the retroviral vector. Fluid samples were centrifuged to obtain distinct samples for stable vector in peritoneal supernatant (vector in peritoneal fluid; Table 2), as well as vector that had entered cells within peritoneal fluid (vector in peritoneal pellet; Table 2). None of the six Phase II patients had any positive vector samples in peritoneal fluid throughout multiple treatment courses, in contrast to Phase I studies in which six of six patients at a similar dose range showed positive vector in peritoneal fluid (2). Table 2 shows that 172 peritoneal fluid samples from Phase II patients were negative for vector by PCR analysis. Although peritoneal fluid samples were uniformly negative in the Phase II
patients, 55% of the peritoneal pellet samples were positive for vector, showing that some gene transfer did occur into transduced cells in Phase II patients. Unlike in Phase I, these levels were too low to detect by Southern blot (data not shown).

Because the vector stability in peritoneal fluid samples from the Phase II patients was dramatically decreased compared with the Phase I results, we analyzed plasma samples for antibody production and peritoneal samples for complement activity to determine whether an enhanced immune response to vector would explain the decreased vector stability. Fig. 2 illustrates the differences in vector stability (Fig. 2A) and antibody formation (Fig. 2B) between Phase I and II patients. Phase I PCR (Fig. 2A, left) shows numerous samples with detectable vector in contrast to Phase II PCR (Fig. 2A, right), in which no vector was detected in this set. The positive controls (462 bp) are found on the right side of each gel (Fig. 2). Western analysis of Phase I peritoneal fluid is represented by samples from patients 1 and 2 with no antibody formation. Lanes 12–15 in Fig. 2B, left lane, contain the negative (12) and positive controls. The arrows indicate the Mß 69,000/70,000 region of interest. The Phase II Western blot, right, is representative of a positive response found in Phase II. Four of six Phase II patients developed antibodies to the retroviral vector envelope, and the other two patients had preexisting antibodies reacting to retroviral envelope. Patients in Phase II developed antibodies to retroviral envelope proteins more rapidly and robustly than did Phase I patients (Table 3). Antibody to viral envelope protein was detected in only 3 of 12 patients (25%, on day 60) in our Phase I BRCA1 gene therapy study. This compared with six of six patients (100%, on day 60) in the Phase II study and was a statistically significant difference (P = 0.025, Fisher exact test). Complement activity is generally low in peritoneal fluid, which provided part of the rationale for i.p. retroviral vector therapy (2). In our prior Phase I study, peritoneal complement levels (CH50) were relatively low and were roughly associated with vector stability (2). As shown in Table 1, peritoneal CH50 levels were significantly increased in the Phase II patients in comparison with the levels in the Phase I patients. These increased levels of complement would likely lead to rapid degradation of i.p. vector and might contribute to antibody formation, given that complement is involved in antigen presentation.

Presence of neutralizing antibodies to retroviral vector was determined by the assay described in “Materials and Methods” in which patient samples were incubated with active LXSN-BRCA1sv vector to determine whether vector titer was decreased by neutralizing activity. Only one Phase I patient had a neutralizing antibody that developed 90 days after treatment, and this was only present in plasma and not in peritoneal fluid. In contrast, four of five Phase II patients had neutralizing antibodies in plasma, and two of these had neutralizing antibodies in peritoneal fluid. This evidence that the high-titer antibodies present in Phase II patients can neutralize retroviral vector in vitro assays provides some evidence that these antivector antibodies may affect vector stability and have in vivo relevance.

Clinical analysis of the Phase II trial included measures of toxicity and clinical responses. Preclinical studies of i.p. LXSN-BRCA1sv injection produced toxicity in immunocompetent mice that developed peritonitis (2). A Phase I trial of BRCA1 gene therapy in patients with ovarian cancer resulted in 25% incidence of self-limiting sterile peritonitis. Of six Phase II patients treated, three developed sterile peritonitis characterized by abdominal discomfort, elevated peritoneal fluid neutrophil count, and fever. In all patients, this was self-limiting and did not cause a delay in treatment schedule. All Phase II patients developed metastatic disease outside the treatment field. Although six patients without a clinical response did not satisfy the planned early-stopping rule, the complete lack of vector stability and marked difference in immune response compared with the Phase I trial led us to stop the trial after consultation with the FDA.

**DISCUSSION**

This study shows that Phase II patients with small-volume ovarian cancer rapidly degrade i.p. retroviral vector, quickly develop neutralizing antibodies to the amphotropic retroviral envelope, and show no clinical response to the therapy. This is in contrast to the results of our prior Phase I trial (2) using the same infusion protocol, which showed stable vector, minimal antibody formation, and some objective response. Although it is difficult to draw definitive conclusions from these small numbers of patients entered nonrandomly in two separate clinical trials, the complete lack of vector stability and development of neutralizing antibodies in Phase II prompted us to terminate the trial.

An important finding from our previous Phase I study of BRCA1 gene therapy for ovarian cancer was low antibody response (25%) and high stability of vector (66%) (2). This is contrasted by 100% antibody response and 0% stability of vector in this Phase II trial. This may be explained by significant differences in immunocompetence between the Phase I and II patients such as differences in tumor, number of previous chemotherapy cycles, and nutritional status. Tumor burden has been shown to affect anergy status possibly by production of growth factors, such as transforming growth factor (17, 18). All patients in the Phase I trial had large tumor masses and extensive carcinomatosis typical for patients with end-stage ovarian cancer. Phase II patients’ tumor burden was much smaller, with no measurable tumor greater

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<th>Table 2 Phase II retroviral vector stability</th>
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* Denotes number of positive samples per number of samples analyzed by PCR.
than 3 cm. Nutritional status, measured by serum albumin, which directly affects immune status, was significantly different between Phase I and Phase II patients. Correlation between serum albumin levels and anergy has been well described (19). Albumin has also been used as a predictor of survival in patients with ovarian cancer (20). Using the independent significant variables of albumin and WBC count, a scatter plot diagram illustrates the distinct difference in the Phase I and Phase II populations of patients (Fig. 1).

These results suggest distinct differences in patient response to i.p. vector injection based on extent of disease and immune response. Greater immunocompetence in Phase II patients is indicated by development of neutralizing antibodies to viral envelope proteins, higher albumin levels, and higher CH50 levels. Because these results were not anticipated, we did not include extensive immunological testing. Future protocols will include multiple assays for humoral and cell-mediated immunity, including anergy skin testing in all patients.

Healthier patients with less extensive disease were treated in the Phase II trial, because Phase I studies showed that i.p. retroviral vector was ineffective against large-volume, bulky disease. Our Phase II results showing that healthier patients with smaller tumors rapidly degrade vector clearly presents a therapeutic quagmire, because the theoretically treatable small-volume disease is apparently associated with vector degradation. Possible strategies for dealing with this dilemma include the development of less immunogenic vectors or coadministration of immunosuppressive agents with retroviral gene therapy in Phase II patients with small-volume disease (21).

Fig. 2  Comparison of Phase I and II ovarian cancer LXSN-BRCA1sv gene therapy PCR results for vector stability and Western blot results for antibody formation. A, vector stability: PCR of peritoneal fluid samples from Phase I and II patients. Peritoneal fluid (100 ml) from each patient was cultured on MCF-7 cells. Cell supernatant was analyzed as described previously (2). Left, Phase I patients; Lanes 1–4, treatment of patient 6 on days 0–3, respectively; Lanes 5–7, third treatment of same patient on days 0–2; Lanes 8–11, third treatment of same patient on days 0–3. Lanes 12 and 13, treatment of patient 2 on days 2 and 3, respectively; Lane 14, 1-kb ladder; Lane 15, positive control; Lane 16, negative control. Right, Phase II patients: patient 2 samples (first seven lanes), blank lane, patient 3 samples (next four lanes), blank lane, patient 4 samples (next four lanes), blank lane, two positive controls, negative control, and the 1-kb ladder. The band of interest is 462 bp. B, Western analysis of patient peritoneal fluid for development of antibodies to retroviral coat proteins, Mr 69,000/70,000 (arrows). Western blots were performed as described previously (2). Left, Phase I patients: Lanes 1–4, patient 1 at day 0, 2 weeks, 4 weeks, and 2 months posttreatment, respectively; Lanes 5–11, patient 2 at day 0, 2 weeks, 4 weeks, and days 1–4 of retreatment; Lane 12, negative control; Lanes 13–15, positive control dilutions of 1:1,000, 1:5,000, and 1:10,000. Right, Phase II patients: first strip, positive control for gp70 protein; second strip, positive control for gp30 protein; third strip, negative control (secondary antibody only). Lanes 1–4, patient 5 at days 1–4 of treatment; Lanes 5 and 6, patient 4 at days 73 and 74; Lanes 7–10, patient 5 on day 31 with serial dilutions of 1:20, 1:67, 1:222, and 1:741.
**ACKNOWLEDGMENTS**

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**REFERENCES**


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