Abstract

Due to the generally slow and incomplete transit of i.p. infused agents into the circulation, treating disease confined to the peritoneal cavity with chemotherapy, biologics, and/or radionuclides provides a pharmacologic advantage. A higher i.p. concentration can be achieved than could be tolerated by systemic administration. An advantage of i.p. versus i.v. administration for localization of radiolabeled antibodies to small peritoneal surface disease has been shown in animal model and human biopsy studies (1, 2). A recent phase III Gynecologic Oncology Group chemotherapy trial has confirmed a survival advantage for i.p. delivery among women undergoing initial therapy for advanced ovarian cancer (3). Although the therapy was more difficult to tolerate such that 60% of patients randomized to the i.p. arm did not complete the entire regimen, there was a 16-month survival advantage. I.p. radionuclide therapy has been used in treatment of ovarian cancer for more than three decades, but side effects have been problematic in non–tumor-targeted 32P therapy (4). Efforts to improve specificity have used a number of antigens expressed on ovarian cancer cells as targets for selective delivery of radionuclide-conjugates. Mouse models and cell culture have been prominent for preclinical study of agents and strategies in the development of i.p. targeted radionuclide therapy for ovarian cancer. Animal studies, which have directed clinical trials, have shown clear improvement in survival with various modifications including combination chemotherapy, pretargeting, and combination of antibodies over simply delivery of a radiolabeled antibody via i.p. route.

Clinical Data

To date, more than five antibodies have been conjugated to four β-emitting radionuclides for i.p. clinical application, and additional conjugates are under study. Experience with i.p. 131I-HMFG1, 131I-A1A1, 186Re-NR-LU-10, 177Lu-CC49, 90Y-CC49, and 90Y-HMFG1 showed some antitumor activity, whether this be palliation of ascites, increased survival, or objective evidence of tumor response (5–8). Some of the most encouraging early results were in women who had a complete response to initial therapy as documented by no evidence of disease at second-look surgery. Despite finding no disease at second-look laparotomy or laparoscopy, it is expected that more than 50% of these patients will fail within the abdominal cavity unless additional treatment is given. Using a single i.p. administration of 90Y-HMFG1 for 25 patients resulted in a 5-year relapse-free survival of 80% versus the expected 50% for control patients who received no further therapy after the negative second-look surgery (9). From limited dosimetry available, 20 to 80 Gy were delivered to tumor with antibody-targeted radionuclide therapy versus surface dose >50 Gy but <20 Gy at 2 mm from nontargeted 32P therapy (10). This encouraging result led to a phase III international trial of 90Y-HMFG1 monoclonal antibody. Unfortunately, no difference in survival or time to relapse has been shown with a median follow-up of 3.5 years in the phase III trial (11).

There are a number of possibilities proposed on why this phase III study failed to show an improved survival for patients who received i.p. radioimmunotherapy. Speculation has included radionuclide choice, the amount of unlabeled antibody, submucosal location of tumor deposits, and the confounding variable of additional consolidation chemotherapy (11). However, those aspects were similar in the Hammersmith group phase II trial and do not explain the superior results from the Hammersmith experience wherein survival at 10 years is higher than in the phase III trial at a median follow-up of 3.5 years (12). The phase III study detected adverse prognostic factors of advanced stage, poorly differentiated tumor, and residual after primary surgery. Although small differences in the proportion of patients with adverse factors, plus the expected advantage of additional consolidation chemotherapy, may have negated detection of a benefit from radioimmunotherapy, it does not account for the poorer outcome for both groups compared with the Hammersmith reports. With 10 of 21 Hammersmith patients treated...
adjuvantly having stage III to IV disease and 5 of 21 having undifferentiated tumors, it is unlikely that they represent a select group with better prognosis than those in the phase III study, but there may be other undefined prognostic factors that were more favorable (13). There may also be undetermined quality control factors in the pathologic assessment and/or preparation/treatment (such as loss of immunoreactivity or low specific activity) that provide an advantage at the well-experienced institution. The phase III results were disappointing and rather surprising in relation to the positive results in the previous phase II experiment. However, a study such as this emphasizes the need to conduct properly controlled, randomized multicenter clinical trials with sufficient patient numbers to achieve statistical significance.

There has been considerable speculation on why the phase III trial failed to show a benefit of 90Y-HMFG1. A key explanation may be that insufficient radiation was delivered as a single administration to achieve tumor clearance.1 Future trials may have more efficacy if the radiolabeled antibody can be delivered repeatedly and in combination with radiation synergistic agents such as chemotherapy.

Three trials of i.p. radiolabeled CC49 anti–tumor-associated glycoprotein 72 antibody have been conducted at the University of Alabama at Birmingham (7, 8). 177Lu was chosen for the initial trial after an animal study showed a superior outcome over 131I (14). In the initial phase I trial, dose escalation used seven dose levels to determine the maximum tolerated dose at 45 mCi/m2. A subsequent trial, aimed at improving the outcome, used interferon to up-regulate target antigen expression and added paclitaxel as a chemotherapeutic with radiosensitizing characteristics. The study found that the full dose of paclitaxel planned (100 mg/m2 i.p.) could be given without compromise of the dose of 177Lu-CC49 that was tolerated with adjuvant interferon (7). Subsequently, a third trial tested substitution of the more energetic β-emitter 90Y for 177Lu (8). Although all three trials were phase I dose escalation studies, objective responses of 8% to 24% were noted in women with measurable disease. Among patients with nonmeasurable disease, 36% to 45% were without evidence of progression for more than 1 year. The difference in progression-free survival has been significant between patients with measurable versus nonmeasurable disease and a minority of patients have had extended progression-free survival for 27 to 96+ months.

Clinical studies suggest that desirable features of a therapeutic radionuclide conjugate include nonimmunogenic antibody-targeting or non–antibody-targeting agent and short plasma half-life of the radionuclide conjugate. Several β- and α-emitting radionuclides are potential candidates for targeted i.p. therapy. Macey and Meredith (15) projected 188Re as the most advantageous among several β emitters for favorable tumor/marrow ratio. This was based on the conjugation to mouse CC49 antibody with a peak plasma uptake at 48 h and an effective plasma half life of ~50 h. This result was from mathematical modeling and has not yet been clinically verified. Favorable features of 188Re include the short physical half-life of 17 h, which allows much of the radioactivity to decay in the peritoneal cavity before reaching the blood circulation, and longer path length than most β emitters. The longer path length than most β-emitting radionuclides may be a potential advantage for treatment of small disease deposits. α particles are promising for minimum volume disease as reported in preclinical and animal studies to date (16). The physical half-life of several α particles is much less than that of 188Re; thus, only an insignificant amount of radioactivity from α-conjugates would be expected to reach the systemic circulation. In that case, local toxicity of peritoneal cavity tissues will likely replace marrow suppression as the dose-limiting toxicity.

Although clinical experience has shown overall improved therapy advantages with i.p. versus i.v. administration for small-volume ovarian cancer in the peritoneal cavity, there are also some disadvantages. These mainly include catheter-related events such as pain, leakage, loculation, infection, and risk of inflammation and/or perforation. Late effects, especially attributed to the radionuclide component of the i.p. treatment, include adhesions and fibrosis. In our series, patients did not require subsequent surgery due to radiation toxicity, but fibrosis was noted in some patients who underwent surgery for other indications.

### Preclinical Models

Several potential enhancements for i.p. therapy of ovarian cancer have been studied in preclinical models (17, 18). For example, the use of a pretargeting scheme and the combination of i.p. administration of CC49 single-chain antibody/streptavidin fusion protein and i.p. dosing of 90Y- or 177Lu-biotin represented a successful therapeutic strategy for treatment of i.p. tumor xenografts (18). New molecules that directly induce apoptosis in tumor cells are available (19). These show activity alone and some have been tested in conjunction with other agents (20, 21). A fresh ovarian cancer tissue slice technique provides a means to mimic the tumor environment, maintaining three-dimensional architecture with stromal and inflammatory cells present. Testing TRA-8 (apoptosis-inducing antibody) in ovarian cancer tissue slices showed a dose-response pattern, with the greatest cell killing at the highest TRA-8 concentration. However, there was considerable variability of sensitivity among 19 patients studied with IC50 values of 6.0 to >1,000 ng/mL (22). With other tumors including breast and cervix, TRA-8 has shown additive and synergistic activity in conjunction with chemotherapy and/or radiation (20, 23). This tissue slice technique may be useful for determining sensitivities to therapeutic agents such that more effective individualized therapy can be undertaken.

### Summary and Conclusions

Animal models and clinical data to date suggest that further improvement in the use of i.p. radionuclide-conjugate therapy for ovarian cancer can be achieved. Advances are expected to include improved targeting antibodies and other novel agents, combination of agents such as radiosensitizing chemotherapy with radionuclide conjugates, integration of various biologics and gene modifications, treatment of small-volume disease, and individualized treatment based on predetermined sensitivity to therapeutic agents.
References


 Brief Overview of Preclinical and Clinical Studies in the Development of Intraperitoneal Radioimmunotherapy for Ovarian Cancer

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