A Phase II Study of Intraperitoneal Radioimmunotherapy with Iodine-131-labeled Monoclonal Antibody OC-125 in Patients with Residual Ovarian Carcinoma

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Abstract

Standard treatment of advanced ovarian cancer is a combination of surgery and chemotherapy. Additional therapies using the i.p. route are considered as a potential means of improving the locoregional control rate. This Phase II study evaluated the efficacy of i.p. radioimmunotherapy (RIT) in patients with minimal residual ovarian adenocarcinoma after primary treatment with surgery and chemotherapy. Between February 1995 and March 1996, six patients with residual macroscopic (<5 mm) or microscopic disease as demonstrated by laparotomy and multiple biopsies received i.p. RIT. All had initial stage III epithelial carcinoma and were treated with debulking surgery and one line (four patients) or two lines (two patients) of chemotherapy. RIT was performed with 60 mg of OC 125 F(ab′)2 monoclonal antibody labeled with 4.44 GBq (120 mCi) of 131I injected 5–10 days after the surgical procedure. Systematic laparoscopy or laparotomy with multiple biopsies performed 3 months after RIT in five patients (clinical progression was seen in one patient) showed no change in three patients and progression in two patients. Toxicity was mainly hematological, with grade III neutropenia and thrombocytopenia in two patients. Human antimoise antibody production was demonstrated in all six patients. This study showed little therapeutic benefit from i.p. RIT in patients with residual ovarian carcinoma.

Introduction

Epithelial ovarian carcinoma is the leading cause of death from gynecological cancer in Europe and the United States (1). Although advances in treatment with cytoreductive surgery and chemotherapy have improved the survival rate in the last decade (2), the prognosis remains poor for patients with advanced-stage disease with a 5-year survival rate of less than 40% for those with stage III disease. For most patients, the standard treatment for advanced-stage disease is a combination of primary debulking surgery and chemotherapy with platinum (cisplatin or carboplatin) and paclitaxel (3). Relapses are mainly locoregional in the abdominal cavity, with a frequency of up to 50% after complete histological response (4).

These observations have led to the development of treatments using the i.p. route for administration of drugs and immuno-specific or non-specific radiopharmaceutical agents (5–8). It has been demonstrated in several Phase I and II trials that i.p. injection of labeled monoclonal antibodies is of some efficacy in microscopic or macroscopic (<5 mm) residual disease (9–21) and that a dose of up to 120 mCi of 131I can be safely administered (13, 14). In this context, we investigated this approach, as added to standard treatment with systematic surgical evaluation, to assess the extent of disease at study entry and the response after RIT.3

Patients and Methods

Between February 1995 and March 1996, six patients (mean age, 60.5 years; range, 55–68 years) with advanced ovarian adenocarcinoma were enrolled in this Phase II study.

Criteria for Inclusion. The inclusion criteria were as follows: (a) stage III epithelial carcinoma with elevated serum CA 125 level; (b) initial treatment with debulking surgery followed by chemotherapy combining platinum (cisplatin or carboplatin) and/or paclitaxel; (c) age <75 years; (d) performance status ≤2; (e) no previous abdominal or pelvic irradiation; (f) normal values for hematological and biochemical parameters; (g) normal abdominopelvic CT; (h) negative HAMA test; and (i) written consent.

Four patients (patients 1–4) had received one line of chemotherapy and showed a normal serum CA 125 level at the time of inclusion. The two other patients (patients 5 and 6) were included after a rise in the serum CA 125 level 3 and 5 months, respectively, after completion of a second line of chemotherapy (Table 1).

The definitive decision for RIT was made after laparotomy and multiple biopsies. Seven biopsies were mandatory, and 13 others were optional, taking into account surgeon and pathologist preferences (Fig. 1). Four of six patients had macroscopic disease (<5 mm), and the other two patients had biopsy-proven microscopic disease.

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3 The abbreviations used are: RIT, radioimmunotherapy; CT, computed tomography; HAMA, human antimouse antibody.
Table 1  Characteristics of the initial treatment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Histopathology</th>
<th>First-line chemotherapy</th>
<th>Second-line chemotherapy</th>
<th>Interval between chemotherapy and RIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Undifferentiated</td>
<td>PA-CP × 6$^{a}$</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Serous</td>
<td>CEP 75 × 6</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Serous</td>
<td>CEP × 4</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Serous</td>
<td>CP × 6</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Serous</td>
<td>CEP 75 × 4</td>
<td>PA × 6</td>
<td>5 mo</td>
</tr>
<tr>
<td>6</td>
<td>Undifferentiated</td>
<td>CEP × 6</td>
<td>PA × 1</td>
<td>3 mo</td>
</tr>
</tbody>
</table>

$^{a}$ PA-CP, paclitaxel (225 mg/m²) and carboplatin (400 mg/m²); CEP, cyclophosphamide (300 mg/m²); epirubicin [75 mg/m² (CEP 75)] or 50 mg/m² (CEP 50); and cisplatin (100 mg/m²); CP, cyclophosphamide (300 mg/m²) and cisplatin (100 mg/m²).

$^{b}$ PA, paclitaxel (175 mg/m²); CCP, cyclophosphamide (300 mg/m²) and carboplatin (400 mg/m²).

$^{c}$ Number of cycles.

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**RIT.** A Tenckhoff catheter was inserted into the Douglas’ cul de sac at surgery. Patients were given Lugol’s solution (30 drops/day) for 3 days before and 6 days after treatment to block thyroid uptake of free $^{131}$I. Before RIT, a scintigraphic evaluation was performed with 74 MBq (2 mCi) of $^{99m}$Tc colloid instilled with 2 liters of saline solution; abdominopelvic distribution was judged satisfactory in all patients. To prevent an anaphylactic reaction, hydroxyrin (1 mg/kg) and ranitidine (150 mg) were given orally as a premedication 1 h before the infusion.

**Radioiodination of OC 125 F(ab')$_2$.** Radioiodination with Na$^{131}$I was performed using the Iodo-Gen method. The specific activity was 2 mCi/mg OC 125 F(ab')$_2$, and the total injected activity was 4.44 GBq (120 mCi). This activity corresponded to the maximal tolerated dose determined previously in a Phase I study using the same antibody and the same radionuclide (13, 14).

Binding of radioiodinated antibodies to the CA 125-immunosorbent column was >70% for all preparations. The radiochemical purity of the preparations, as controlled by electrophoresis, was >95%. With 3% human serum albumin in 18 ml of PBS (pH 7.0), the preparations stored at −20°C were stable for 4 days.

RIT was performed from 5–10 days after surgery. Patients received 2 liters of saline solution for 30 min, followed by the infusion of 60 mg of OC 125 F(ab')$_2$ labeled with 4.44 GBq (120 mCi) of $^{131}$I for 15–30 min. Patients were then instructed to change position every 15 min for 2 h to obtain a homogeneous i.p. distribution of labeled monoclonal antibodies. During the infusion, patients were monitored for vital signs and adverse reactions every 15 min and then cared for in a radiation-controlled environment until the dose rate was less than 0.25 millirem (2.5 μSv) at a distance of 1 meter from the patient (mean time, 11 days; range, 8–14 days).

**Response.** Tumor response was assessed 3 months after RIT by laparoscopy or laparotomy, unless patients had clinically, progressive disease, and/or by CT. Surgery was performed by the same surgeon. The procedure consisted of laparoscopy, which was followed by laparotomy in patients without macroscopic disease. Therefore, patients had either biopsies of macroscopic tumor foci under laparoscopy or multiple biopsies by laparotomy, as for inclusion.

Responses were classified as follows: (a) complete (no macroscopic disease at laparotomy and negative multiple biopsies); (b) partial (regression from macroscopic to microscopic disease); (c) no change (unchanged macroscopic or microscopic disease without any new lesions); and (d) progressive (progression from microscopic to macroscopic disease).

**Toxicity.** Toxicity was scored according to the WHO classification. After RIT, patients were seen at days 15, 30, and...
parameters, and liver tests. 

Results

Clinical examination, CA 125 level, hemogram, biochemical parameters were assessed at days 14, 28, and 60.

HAMA response was tested on blood samples collected before RIT and at days 14, 28, 60, and 90.

Follow-up. After RIT, patients were followed-up every 3 months for 2 years and then every 6 months. This included clinical examination, CA 125 level, hemogram, biochemical parameters, and liver tests.

Results

None of the five patients who underwent surgical evaluation achieved a complete response; three had stabilization (patients 2, 3, and 6) and two had progression from microscopic to macroscopic disease (patients 1 and 5). Patient 4 had no surgery because of progression on CT. After failure of RIT, all patients immediately received various regimens of chemotherapy. Five patients died between 8 and 22 months after RIT, and 1 patient is still alive with progressive disease 34 months after RIT (Table 2).

Table 2 Disease status at the time of RIT and follow-up

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Surgical findings at inclusion*</th>
<th>Surgical findings at evaluation</th>
<th>Post-RIT therapy</th>
<th>Clinical status (survival time after RIT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Microscopic</td>
<td>Macroscopic</td>
<td>PA-CP × 6</td>
<td>Dead of disease (13 mo)</td>
</tr>
<tr>
<td>2</td>
<td>Macroscopic (&lt;5 mm)</td>
<td>Macroscopic (&lt;5 mm)</td>
<td>PA × 3</td>
<td>Dead of disease (8 mo)</td>
</tr>
<tr>
<td>3</td>
<td>Macroscopic (&lt;5 mm)</td>
<td>Macroscopic (&lt;5 mm)</td>
<td>PA × 6</td>
<td>Alive with disease (34 mo)</td>
</tr>
<tr>
<td>4</td>
<td>Macroscopic</td>
<td>Not done*</td>
<td>PA-CP × 6</td>
<td>Dead of disease (22 mo)</td>
</tr>
<tr>
<td>5</td>
<td>Microscopic</td>
<td>Macroscopic</td>
<td>PA-E × 6</td>
<td>Dead of disease (22 mo)</td>
</tr>
<tr>
<td>6</td>
<td>Macroscopic (&lt;5 mm)</td>
<td>Macroscopic (&lt;5 mm)</td>
<td>Melphalan × 10 × 4</td>
<td>Dead of disease (18 mo)</td>
</tr>
</tbody>
</table>


PA-CP, paclitaxel (225 mg/m²) and carboplatin (400 mg/m²); PA, paclitaxel (175 mg/m²); PA-E, paclitaxel (225 mg/m²) and epirubicin (50 mg/m²); C-CP, cyclophosphamide (300 mg/m²) and carboplatin (400 mg/m²).

Discussion

The main cause of failure in advanced ovarian cancer is locoregional recurrence, with patients ultimately dying from refractory ascites and ileus (3). Therefore, the use of the i.p. route would appear to be a suitable approach for improving the therapeutic index by increasing the bioavailability of drugs or labeled monoclonal antibodies in the abdominal cavity and reducing their circulating levels and hence their toxic side effects.

The superiority of i.p. chemotherapy has been demonstrated in a randomized trial in which survival was improved for patients who received i.p. cisplatin as compared with i.v. cisplatin (plus cyclophosphamide in two arms) for stage III ovarian carcinoma and residual tumor <2 cm (5). Animal and clinical studies have shown higher tumor uptake with labeled monoclonal antibodies for the i.p. route than for the i.v. route (22, 23). The role of tumor volume in the efficacy of RIT has been demonstrated in vitro and in vivo studies (24). In a cohort of patients with ovarian carcinoma who underwent surgery as a part of their treatment 24–72 h after receiving an i.p. injection of 111mIn-labeled OC 125, Chatal et al. (25) reported higher tumor uptake in malignant cell clusters and small tumors (<5 mm) than in tumors >5 mm. These results were confirmed by therapeutic clinical studies that showed no response in macroscopic tumors >2 cm, 20% complete remission in tumors <2 cm, and 50% complete remission in microscopic disease (9–21). However, the interpretation of these results was complicated by a lack of homogeneity in the methods used to evaluate response to treatment. Finally, contradictory results have been reported for patients who had histological and/or cytological evaluation of response (10, 15).

This led us to conduct a Phase II trial with a rigorous systematic histological evaluation. Laparotomy was considered essential for patients included in the study to achieve complete exploration of the abdominal cavity and provide multiple biop-
peritoneal washing, avoided the risk of overlooking patients the extent of the disease and the response after RIT, was very ethical considerations, and the protocol was discontinued. These statistical probabilities were regarded as secondary to logical response. This rigorous protocol, which included surgery to assess the extent of the disease and the response after RIT, was very demanding for patients, which accounts for the small number of cases. In fact, the treatment might have had a certain degree of efficacy in a larger cohort. If the real response rate were 20%, an absence of response in six patients would represent a 26% chance of an incorrect estimate of treatment efficacy. However, these statistical probabilities were regarded as secondary to ethical considerations, and the protocol was discontinued.

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The main explanation for the failure of i.p. RIT was probably the presence of i.p. adherences preventing homogeneous distribution of radiolabeled monoclonal antibodies in the abdominopelvic cavity. This problem has been reported in studies of i.p. 32P. In a Norwegian trial (7), 16.5% of patients did not receive this treatment because of adherences. This major problem might be overcome if several catheters were inserted into the abdominopelvic cavity and if treatment were performed immediately after laparotomy (thus before adherence formation).

This study was too small to question the results achieved in series with larger numbers of patients. The rigor of this protocol made it too demanding, but the first part, which included laparotomy with biopsies, could be used for future protocols because it is probably the best method to evaluate disease status in ovarian carcinoma.

Acknowledgments

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References


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