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Single-dose Intraperitoneal Radioimmunotherapy with the Murine Monoclonal Antibody I-131 MOv18: Clinical Results in Patients with Minimal Residual Disease of Ovarian Cancer

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Sixteen of 19 enrolled patients with minimal residual disease of ovarian cancer (macroscopic disease <5 mm or positive blind biopsies and/or positive peritoneal washing), demonstrated by surgical second-look, underwent intraperitoneal radioimmunotherapy (RIT) with the radiolabelled monoclonal antibody I-131 MOv18 (mean dose 14 mg of MOv18 with 3700 GBq of I-131) 30–40 days after the second-look procedure. Clinical follow-up and/or third-look evaluation performed 90 days after RIT showed complete response (CR) in 5 patients, no change (NC) in 6 patients and progressive disease (PD) in 5 patients. Follow-up study showed long-term maintained CR in 1 patient (34 months) and relapses in the other 4 patients after a mean disease-free period of 10.5 months. 5 NC patients showed clinical or instrumental progression after a mean disease-free period of 13 months. The toxicity of RIT was negligible. Only 1 patient showed mild and transient bone marrow suppression (platelet count nadir 52 000 mm^3 after 30 days). HAMA production was demonstrated in 94% (15/16) of patients. In conclusion, RIT appears to be a very promising therapeutic approach to treat minimal residual disease of ovarian cancer.

Key words: ovarian cancer, monoclonal antibodies, radioimmunotherapy
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INTRODUCTION

OF ALL GYNAECOLOGICAL tumours, ovarian cancer is the leading cause of death due to its biological aggressiveness and often delayed diagnosis. Cytoreductive surgery followed by first line chemotherapy produces combined response rates of 65–80% [1–3], and increases the overall median survival. However, at least 50% of patients with complete responses eventually relapse [4] and second-line chemotherapy for refractory or recurrent disease gives poor results, with a response rate of 5–19% [5]. Therefore, further progress in treating ovarian cancer will depend on developing a treatment modality that can eradicate residual disease after surgery and chemotherapy.

In recent years, various phase I–II clinical trials with monoclonal antibodies, coupled with therapeutic activity of appropriate radionuclides (radioimmunotherapy, RIT), have been carried out; RIT was used as palliative or adjuvant therapy in several human tumours with encouraging results, particularly in ovarian cancer [6–8].

The aim of our study was to evaluate the efficacy and toxicity of RIT as second-line treatment of residual ovarian cancer using I-131 labelled MOv18, a well-known monoclonal antibody with restricted specificity against ovarian cancer [9]. Based on the conclusions of several biodistribution studies with radiolabelled monoclonal antibodies, we tried to optimise RIT by using the intraperitoneal route of administration [10, 11] and selecting a very small tumour target [12–14], i.e. minimal residual disease of ovarian cancer after primary treatment. We used laparoscopy or laparotomy both to assess the extent of disease and the response of RIT (Table 1). This study was approved by the National Cancer Institute Ethics Committee, and written informed consent was obtained from all patients.

MATERIALS AND METHODS

Monoclonal antibody I-131 MOv18

MOv18 is a murine monoclonal antibody which recognises a membrane folate-binding glycoprotein of 38 KDa and reacts with approximately 90% of epithelial ovarian carcinomas [15]. MOv18 has been labelled with I-131 (Iodo Gen method) by Sorin Biomedica (Italy) and its *in vivo* distribution has been evaluated in 30 patients with advanced ovarian cancer [16]. This study demonstrated that MOv18 is a suitable monoclonal antibody for

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Table 1. Design of the study

- Patients with advanced epithelial ovarian cancer (III stage, FIGO classification)
- Primary therapy with cytoreductive surgery and first-line chemotherapy (cisplatin-based regimens)
- Minimal residual disease shown by surgical second-look (laparoscopy or laparotomy)
- Intraperitoneal RIT with I-131 MOv18 (30–40 days after second-look) applying the following procedures:
  - Lugol solution (5%) treatment
  - Insertion of intraperitoneal catheter
  - Tc-99m MAA abdominal scintigraphy
  - I-131 MOv18 i.p. administration
  - Active movements by the patient for about 2 h
  - Catheter removal and scintigraphic examination at 96 h
- Clinical and instrumental follow-up (surgical third-look 90 days after RIT)

the *in vivo* radiolocalisation of ovarian cancer lesions (sensitivity 73%, specificity 100%), with better biodistribution following intraperitoneal administration.

Patients

Nineteen patients (mean age 57, range 27–70), with Stage III (FIGO classification) serous ovarian carcinomas at first diagnosis were enrolled in this study (Table 2). They all had minimal residual disease (MRD) of ovarian carcinoma, demonstrated by second-look evaluation performed following cytoreductive surgery and first-line chemotherapy. MRD was characterised by two well-defined, alternative conditions: (1) *macroscopic disease* consisting of histologically confirmed tumour lesions smaller than 5 mm (10 patients); (2) *microscopic disease* demonstrated by positive blind biopsies and/or positive peritoneal washing. Both are rare conditions occurring in 7–10% of patients (authors' unpublished data) after primary treatment for advanced ovarian cancer.

RIT was not performed in Patient 4 due to sudden and progressive tumour ascites and in Patients 12 and 19 because of non-homogeneous abdominal perfusion shown by scintigraphy before RIT.

All patients submitted to RIT were in fairly good clinical condition (Karnofsky score ≥90), with normal values of routine haematological and biochemical parameters. Following RIT, the patients underwent monthly clinical and instrumental check-ups.

Radioimmunotherapy

RIT was planned 30–40 days after the second-look procedure. Patients were nursed in a radiation-controlled area for 5 days following radiocompound administration. The thyroid uptake of free iodine was blocked by means 5% Lugol solution (30 drops twice a day, starting 3 days before RIT and continued for the following 10 days). A catheter was inserted into the peritoneal cavity under local anaesthesia and, before RIT, scintigraphic evaluation of the abdominal perfusion was performed with 111 MBq of Tc-99m MAA washed with 500 ml of saline solution. Only patients with a homogeneous abdominal distribution of the radiotracer (view of all abdominal quadrants and pelvic cavity) received the therapeutic dose of I-131 MOv18.

Table 2. Extent of minimal residual disease (MRD) in the patients enrolled in the study

Patient	First-line CT*	2nd Look	MRD Extent	Site of lesions† or positive biopsies	Peritoneal Washing
1	AP	LPS	Macroscopic	Diaphragm	Pos
2	P	LPS	Macroscopic	Diaphragm	Pos
3	P	LPS	Microscopic	—	Pos
4	CP	LPT	Macroscopic	Diaphragm, bowel, pelvic peritoneum	Pos
5	P	LPS	Macroscopic	Pelvic peritoneum	Pos
6	CP	LPT	Microscopic	Omentum, right para-colic gutter	Pos
7	CP	LPT	Microscopic	—	Pos
8	CP	LPT	Microscopic	Diaphragm, pelvic peritoneum	Pos
9	P	LPT	Macroscopic	Bowel	Neg
10	CP	LPS	Microscopic	Right para-colic gutter	Neg
11	P	LPT	Macroscopic	Omentum, bowel	Pos
12	P	LPT	Microscopic	—	Pos
13	CP	LPT	Microscopic	—	Pos
14	P	LPT	Microscopic	—	Pos
15	P	LPS	Macroscopic	Right para-colic gutter	Pos
16	CP	LPT	Macroscopic	Omentum, pelvic peritoneum	Neg
17	CP	LPS	Macroscopic	Diaphragm	Neg
18	CP	LPS	Microscopic	Bowel	Neg
19	P	LPT	Macroscopic	Abdominal peritoneum	Neg

* Cisplatin based chemotherapeutic regimens used as first-line chemotherapy.

† Macroscopic lesions <5 mm, histologically confirmed. LPS, laparoscopy; LPT, laparotomy; AP, doxorubicin (60 mg/m^2 × 3 courses) and cisplatin (1 mg/kg × 7 courses); P, cisplatin (50 mg/m^2 × 9 courses); CP, cyclophosphamide (750 mg/m^2 × 6 courses) and cisplatin (75 mg/m^2 × 6 courses).

Each patient was treated intraperitoneally with a mean dose of 14 mg of MOv18 (range 8–21 mg) labelled with 3700 MBq of I-131, diluted in approximately 2 l of saline solution to enhance its distribution within the peritoneal cavity. Patients were then instructed to change position every 15 min for 2 h to obtain an even intraperitoneal distribution of I-131 MOv18. Before discharging the patient, the intraperitoneal catheter was removed and a scintigraphic examination was performed to evaluate the I-131 MOv18 distribution.

Response

Laparotomy or laparoscopy (third-look) was used to assess tumour response 90 days after treatment unless patients had already developed progressive disease clinically. The choice of the third-look procedure was made by the surgeon considering the patient's age, the clinical condition of the patient and the residual disease after debulking surgery (laparoscopy for tumour >2 cm and laparotomy for tumour <2 cm). Pre- and post-RIT evaluations were performed by the same surgeon to facilitate the evaluation of the RIT results. The visual assessment of the peritoneal cavity included histological examination of macroscopic lesions as well as random biopsies and peritoneal lavage with normal saline for cytological assessment (peritoneal washing).

Responses were classified as:

(i) complete response (CR), given by a completely negative third-look (macroscopic examination, biopsies and peritoneal washing);
(ii) no change (NC), given by the persistence of macroscopic or microscopic tumour foci as shown on second-look without any new lesions;
(iii) progressive disease (PD), given by macroscopic or microscopic tumour progression.

Toxicity

Patients were examined monthly after RIT to assess toxicity. The routine haematological and biochemical parameters were evaluated. Antibody response to the murine MOv18 (HAMA, Human Anti-Mouse Antibody) was assessed with a semi-quantitative immunometric assay on blood samples collected before RIT and after 30–45 days.

RESULTS

RIT gave complete responses (CR) in 5/16 patients (31%) and no-change (NC) responses in 6/16 (38%) patients. The remaining 5 patients (31%) did not respond to treatment and were classified as PD 4 with quick tumour progression within 1–2 months after RIT and, therefore, not subjected to third-look procedures.

Of the CR patients, 1 patient was still alive and disease-free at 34 months, while the other 4 patients relapsed after a mean disease-free period of 10.5 months (range 3–16 months). Two of these patients (5 and 15) failed outside the field of RIT irradiation (left inguinal and supraclavicular node metastasis). The relapsed patients were submitted to different chemotherapeutic regimes with the following results. Two patients were alive and disease-free at 31 and 38 months, 1 patient was alive with pelvic relapse at 24 months and 1 patient died of tumour progression (survival time 24 months).

Of the 6 NC patients, 1 patient was still alive and disease-free at 25 months, while the other 5 patients showed clinical or instrumental progression after a mean interval of 13 months (range 3–23 months), after which they were submitted to various chemotherapeutic regimes with the following results. One patient was alive and disease-free at 31 months, 3 patients were alive with tumour at 24, 28 and 34 months and 1 patient died of tumour progression (survival time 15 months).

5 PD patients did not respond to RIT and 4 died of tumour progression after a mean survival time of 7 months (range 5–11

Table 3. Results of radioimmunotherapy and follow-up

Patient	Third-look	Response	Site of first relapse (Time in months)		Post-RIT therapy	Response	Clinical status (Survival in months)	
1	NP	PD	—				Dead	(5)
2	NP	PD	—				Dead	(6)
3	LPS	PD	—				Dead	(11)
5	LPS	CR	Inguinal node	(12)	C+E	CR	Disease-free	(38)
6	LPT	NC	Abdomen	(3)	C+T	NC	Alive with tumour	(34)
7	LPT	CR	—			CR	Disease-free	(34)
8	LPT	CR	Pelvis	(16)	C+E	CR	Disease-free	(31)
9	LPS	NC	Retroperitoneal nodes, pelvis	(23)	T	CR	Disease-free	(31)
10	LPT	NC	Pelvis	(13)	C+P	PR	Alive with tumour	(28)
11	LPS	NC	Abdomen	(12)	C		Dead	(15)
13	LPS	NC					Disease-free	(25)
14	LPT	CR	Ascites, abdomen	(11)	C	NC	Dead	(24)
15	LPS	CR	Supraclavicular node	(3)	T+Ext Radiotherapy	CR	Alive with pelvic relapse and retroperitoneal nodes	(24)
16	NP	PD	—				Dead	(7)
17	LPS	NC	Abdomen	(14)	P+T	PR	Alive with tumour	(24)
18	NP	PD	—		C	CR	Alive with tumour	(6)

* Different chemotherapeutic regimens used as post-RIT treatment.

Third-Look: NP, not performed; LPS, laparoscopy; LPT, laparatomy. Result: PD, Progressive disease; CR, complete response; NC, no change. C, carboplatin (300–500 mg/m^2) × 3–5 courses; E, epirubicin (90 mg/m^2) × 5 courses; P, cisplatin (1–5 mg/m^2) × 6–9 courses; T, taxol (175 mg/m^2) × 3–8 courses.

months). Patient 18 was still alive with tumour after second-line chemotherapy at 6 months.

As regards the toxicity of RIT, the administration of I-131 MOv18 was not followed by any acute clinical symptoms, and during follow-up only 1 patient showed mild bone marrow toxicity (platelet count nadir 52 000/mm^3 after 30 days) with spontaneous recovery. Moreover, the surgical third-look procedures never showed abdominal adhesions that were attributable to RIT.

With regard to the immunogenicity of the murine MOv18, HAMA levels were negative in all patients before RIT; after 45 days 15/16 (94%) patients had developed immune response with increasing titres of HAMA.

DISCUSSION

RIT is probably the most attractive clinical application of radiolabelled monoclonal antibodies in the field of oncology [17]. In spite of its theoretical advantages compared with external beam irradiation, clinical applications of RIT are still limited owing to problems in the current immunoreagent biodistribution in humans, with related poor radiation doses to the tumour lesions and the risk of high radiation-dose to health organs [18]. A number of clinical studies have clearly showed the biodistribution to be improved after loco-regional administration of the radiocompound [10, 11]. Moreover, the choice of a very small tumour target for RIT is particularly important to obtain high radiation doses to the tumour [12].

According to these assumptions, ovarian cancer seems one of the most suitable fields of application for RIT. It is a very aggressive cancer which needs improvements in the therapeutic modalities; the intracavitary route of administration can be used because the tumour remains confined to the abdominal cavity for most of its natural history, and it is a very good target for RIT as minimal residual disease.

RIT's potential to obtain therapeutic responses with acceptable toxicity in ovarian cancer has already been demonstrated by several trials which, however, are very heterogeneous, both in the criteria of patient selection and in the methods used to evaluate RIT efficacy [6–8].

By contrast, in our study, we used very restricted and homogeneous criteria for the patient selection, and the assessment of RIT efficacy was performed by the same surgeon who performed the second-look with surgical and histological examination of the abdominal cavity and prolonged and accurate follow-up.

In our study, RIT gave surgically proven CR in 31% of patients. This result is superior to the CR rates (5–19%) reported with intravenous second-line chemotherapy [5]. With intraperitoneal administration of cisplatin, surgically proven response rates of 20–30% have been reported [19], but RIT appears to be less toxic and a more easy treatment modality than intraperitoneal chemotherapy.

As it was difficult to accurately determine minimal regression or stable disease of MRD with laparoscopy or laparotomy, we cautiously categorised patients with an apparently stabilised situation as NC. Nevertheless RIT seemed to control tumour proliferation in such patients, as was demonstrated by the comparison between the interval (mean 13 months) before clinical evidence of tumour relapse in NC patients and the very short survival time (mean 7 months) of PD patients.

Moreover, it is interesting to note that even in our study, characterised by a very homogeneous patient population, a correlation between RIT efficacy and disease extent was observed. 3 of the 5 patients with CR responses had microscopic disease, while 3 of the 5 PD cases had macroscopic disease.

The main potential toxicity of RIT is myelosuppression which is related to the radiation dose to the bone marrow. In our study, we observed mild bone marrow toxicity in only 1 patient, and the acceptable toxicity of RIT was further demonstrated by the feasibility of salvage chemotherapy in 10 patients who relapsed during follow-up: only 4 patients showed grade 3–4 falls in neutrophil or red blood cell counts (WHO classification).

Finally, the clinical outcomes of our study acquire even more importance if we consider that they have been obtained with a single cycle of treatment and using I-131, which cannot be considered the best radionuclide for RIT [20, 21]. In view of the negligible toxicity and the absence of peritoneal adhesions after RIT, it would be reasonable, therefore, to plan serial cycles of RIT to increase its efficacy. However, successful serial RIT is currently compromised by the immunogenicity of murine monoclonal antibodies such as MOv18, which provokes HAMA responses in most of the treated patients (94% in our study). In fact, HAMA forms complexes with murine antibodies which are quickly eliminated by the reticuloendothelial system, thus reducing the radiation doses to the tumour target. The solution to this problem is expected from progress in immunology with the development of less immunogenic molecules, such as chimeric, humanised or completely human monoclonal antibodies. However, it has to be considered that the therapeutic efficacy of RIT with murine monoclonal antibodies could be partially attributed to the activation of the immune system with resultant antitumour effects [22, 23]. As a result, the use of chimeric, humanised or human monoclonal antibodies could be less effective than murine monoclonal antibodies. Finally, progress is also required in the choice of radionuclide and labelling techniques, using monoclonal antibody radiolabelled with beta or alpha-emitters.

In conclusion, the important results obtained in our study allow us to consider RIT as a very promising experimental second-line therapy for the management of ovarian cancer. The above-mentioned advances in radiochemistry and immunology could enable RIT to join the conventional therapies for ovarian cancer; its major potential would be the eradication of residual disease after primary therapies.

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Prognostic Factors for Survival After Breast Conserving Therapy for Stage I and II Breast Cancer. The Role of Local Recurrence

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Risk factors for local recurrence (LR) in a univariate analysis had a significant correlation with survival. Local and distant failure could not be regarded as independent events. We undertook a multivariate survival analysis to study the relation between LR and survival. In a retrospective study of 1026 patients treated with tumorectomy, axillary dissection and radiotherapy, factors associated with disease-specific survival (DSS) were analysed. Actuarial estimates for DSS are 91% at 5 years and 86% at 10 years. The multivariate analysis revealed five factors: clinical stage, number of affected axillary nodes, histological grade, degree of tubule formation and left-sided primary tumour. Controlling for these factors, LR appeared to be significantly correlated with DSS. The hazard rate of DSS was estimated to increase by a factor 8.8 (95% confidence interval 4.6–16.8) upon occurrence of a LR. Local recurrence *per se*, apart from the identified prognostic factors, is a risk factor for DSS. The exact mechanism by which LR has an influence on survival cannot be clarified from these data.
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INTRODUCTION

RANDOMISED STUDIES comparing breast-conserving treatment (BCT) with radical or modified radical mastectomy for the local treatment of early (stage I and II) breast cancer have shown little difference in survival. Local tumour excision followed by irradiation also renders acceptable 5-year local control rates comparable with those after mastectomy [1–3]. The application of radiotherapy after local excision appears to be of major importance for local control, but the high local recurrence (LR) rates observed in non-irradiated patients seem to have no significant influence on survival [2, 4, 5]. This finding contrasts with the poor survival that is generally seen following LR after