Adjuvant therapy of ovarian cancer with radioactive monoclonal antibody

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Summary Fifty-two patients with epithelial ovarian cancer were treated with yttrium-90-labelled monoclonal antibody HMF61 administered intraperitoneally following conventional surgery and chemotherapy as part of an extended phase I–II trial. The treatment was well tolerated and the only significant toxicity observed was reversible myelosuppression as previously described. Following conventional surgery and chemotherapy, 21 out of the 52 patients had no evidence of residual disease and were regarded as receiving treatment in an adjuvant setting. To date, two of these patients have died of their disease (follow-up 3–62 months, median follow-up 35 months).

This extended phase I–II study suggests that patients with advanced ovarian cancer who achieve a complete remission following conventional therapy may benefit from further treatment with intraperitoneal radioactive monoclonal antibody.

Cancer of the ovary ranks sixth as a fatal form of cancer in women (Young et al., 1982). Its incidence is approximately 20 per 100,000 with 4,500 new cases and 3,700 deaths per annum in the United Kingdom (Department of Health 1987). At diagnosis most patients have tumour outside the pelvis and this probably accounts for the poor prognosis (FIGO news report 1971). Advances in cytoreductive surgery and postoperative chemotherapy in the last decade have produced response rates of 65–80% but only a small improvement in overall survival (Neijt et al., 1984). Unfortunately, most patients relapse and die of their disease indicating that benefits from surgery and chemotherapy, whether these may be new drugs or new combination of old drugs have reached a plateau (Marsoni et al., 1990).

More than 90% of epithelial ovarian tumours express high levels of many antigens (Bast et al., 1991), including one in particular, known as polymorphic epithelial mucin (PEM) (Gendler et al., 1987). PEM can be described as a 'tumour associated antigen' because although expressed extensively by many epithelial cancers it can also be found at low levels on many normal tissues (Arkile et al., 1981). Several monoclonal antibodies to this antigen and its various epitopes have been made and used for in vitro and in vivo diagnosis of many cancers including ovarian cancer (Epenetos et al., 1982; Pateisky et al., 1985; Colcher et al., 1983). Since 1983, we have been investigating the possibility of tumour targeting and therapy by the intraperitoneal administration of radiolabelled monoclonal antibodies in patients with ovarian cancer (Epenetos et al., 1984).

We have previously described extensively the pharmacokinetics, biodistribution and toxicity of iodine-131 and yttrium-90-labelled monoclonal antibodies for the treatment of ovarian cancer (Epenetos et al., 1987; Stewart et al., 1989, 1990; Maraveyas et al., 1993). In this report we present the first comprehensive survival data of patients treated in this way from October 1987 to December 1992. Based on our results we propose that this novel modality should now be considered further as a form of adjuvant in patients with cancer of the ovary.

Patients, materials and methods

Patients
Fifty-two patients with known epithelial cancer received intraperitoneal radioimmunotherapy with yttrium-90-labelled monoclonal antibody HMF61. Patients' ages ranged from 29–76 years. All had performance status above WHO Grade 2. All patients had previously undergone cytoreductive surgery, and all but one were subsequently treated with cisplatin or carboplatin based chemotherapy. One patient (Stage Ic) did not receive chemotherapy. Table I shows the stage and disease status at presentation of all treated patients and Table Ib shows the histology and stage of patients treated as adjuvant, as assessed at second look laparoscopy. It can be seen that there are 22 patients who had no evidence of disease at the time of laparoscopy. One (Stage Ia) was disease free following chemotherapy for relapse and the remaining 21 were regarded as receiving treatment in an adjuvant setting.

Monoclonal antibody
The monoclonal antibody used in this study was Human Milk Fat Globule 1 (HMF61) (ICRF, London and Unipath (UK) Ltd, Bedford). HMF61 is a mouse IgG1 monoclonal antibody that binds to the PEM molecule found on more than 90% of epithelial ovarian carcinomas (Arkile et al., 1981). Patients received 25 mg of antibody.

Antibody labelling
Yttrium-90 (AERE Harwell, UK) was chelated to the antibody-DTPA, CITC-DTPA or DOTA conjugate as previously described (Stewart et al., 1990; Meares et al., 1990). Free radioisotope was removed by sephadex G50 gel filtration using phosphate buffered saline as elution buffer. Specific activity of radiolabelled antibody was <5 Ci mg⁻¹. The final dose of administered antibody was made up to 25 mg of total IgG by adding unlabelled HMF61 IgG to the radiolabelled fraction. Antibody immunoreactivity was tested in an enzyme-linked immunosorbant assay (ELISA method) before and after radiolabelling and was compared with undervatised antibody using micro titre plates coated with purified antigen. No obvious reduction in immunoreactivity was seen. The administered dose of radioactivity was measured in a SIEL isotope calibration chamber that had been calibrated with an yttrium-90 source (Stewart et al., 1990).

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Received 2 November 1992; and in revised form 1 April 1993.
Table 1a Patient’s number, FIGO stage and extent of disease at antibody treatment

| Patient no. | FIGO stage at presentation | Disease stage at antibody therapy |
|-------------|----------------------------|----------------------------------|
| 1           | 1a                         | No evidence of disease following relapse |
| 2           | 1a                         | Bulky* disease + ascites          |
| 3           | 1c                         | No evidence of disease            |
| 4           | 1c                         | No evidence of disease            |
| 5           | 1c                         | Positive peritoneal washings      |
| 6           | 1c                         | No evidence of disease            |
| 7           | 2a                         | Unassessable adhesions            |
| 8           | 2b                         | No evidence of disease            |
| 9           | 2b                         | No evidence of disease            |
| 10          | 2c                         | No evidence of disease            |
| 11          | 2c                         | No evidence of disease            |
| 12          | 3                           | No evidence of disease            |
| 13          | 3                           | No evidence of disease            |
| 14          | 3                           | Unassessable adhesions            |
| 15          | 3                           | Bulky disease                     |
| 16          | 3                           | Bulky disease                     |
| 17          | 3                           | Bulky disease                     |
| 18          | 3                           | Bulky disease                     |
| 19          | 3                           | Minimal* disease                  |
| 20          | 3                           | Minimal disease                   |
| 21          | 3                           | Bulky disease                     |
| 22          | 3                           | Bulky disease                     |
| 23          | 3                           | Bulky disease                     |
| 24          | 3                           | No evidence of disease            |
| 25          | 3                           | Bulky disease                     |
| 26          | 3                           | Minimal disease                   |
| 27          | 3                           | Unassessable adhesions            |
| 28          | 3                           | Bulky disease                     |
| 29          | 3                           | No evidence of disease            |
| 30          | 3                           | No evidence of disease            |
| 31          | 4                           | No evidence of disease            |
| 32          | 4                           | No evidence of disease            |
| 33          | 4                           | Extra peritoneal disease          |
| 34          | 4                           | No evidence of disease            |
| 35          | 4                           | Bulky disease                     |
| 36          | 4                           | Bulky disease                     |
| 37          | 4                           | Minimal disease                   |
| 38          | 4                           | Bulky disease                     |
| 39          | 4                           | Minimal disease                   |
| 40          | 4                           | Bulky disease                     |
| 41          | 4                           | Minimal disease                   |
| 42          | 4                           | Minimal disease                   |
| 43          | 4                           | No evidence of disease            |
| 44          | 4                           | No evidence of disease            |
| 45          | 4                           | No evidence of disease            |
| 46          | 4                           | Unassessable                      |
| 47          | 4                           | No evidence of disease            |
| 48          | 4                           | Unassessable                      |
| 49          | 4                           | Bulky disease                     |
| 50          | 4                           | Bulky disease                     |
| 51          | 4                           | No evidence of disease            |
| 52          | 4                           | No evidence of disease            |

* Bulky disease = > 2 cm.  Minimal disease = < 2 cm.

Table 1b FIGO stage and histology of patients treated in an adjuvant setting

| No. | Stage at presentation | Histology                  |
|-----|-----------------------|----------------------------|
| 1   | Ic                    | Endometrioid               |
| 2   | Ic                    | Endometrioid               |
| 3   | Ic                    | Serous                     |
| 4   | IIb                   | Undifferentiated           |
| 5   | IIb                   | Serous                     |
| 6   | IIc                   | Undifferentiated           |
| 7   | IIc                   | Endometrioid               |
| 8   | III                   | Endometrioid               |
| 9   | III                   | Endometrioid               |
| 10  | III                   | Undifferentiated           |
| 11  | III                   | Endometrioid               |
| 12  | IV                    | Undifferentiated           |
| 13  | IV                    | Serous                     |
| 14  | IV                    | Serous cystadenocarcinoma  |
| 15  | IIa                   | Clear cell                 |
| 16  | Ic                    | Serous cystadenocarcinoma  |
| 17  | IIc                   | Well differentiated        |
| 18  | III                   | Serous                     |
| 19  | III                   | Undifferentiated           |
| 20  | III                   | Serous                     |
| 21  | III                   | Endometrioid               |

Pharmacokinetics

Pharmacokinetics, toxicity and dosimetry have been previously reported (Epenot et al., 1987; Stewart et al., 1989, 1990; Maraveyas et al., 1993). Approximately 30% of the intraperitoneally injected immunoconjugate was absorbed into the systemic circulation by 48 h after administration (Stewart et al., 1989, 1990; Maraveyas et al., 1993).

Results

Toxicity

The treatment was well tolerated by all patients. Reversible myelosuppression was observed at high doses (>15 mCi of HMFG1-DTPA-90Y). This toxicity was reduced considerably by the subsequent use of more stable chelating agents known as DOTA and CITC-DTPA (Moi et al., 1990). No significant myelotoxicity was observed even at higher doses of up to 20 mCi of HMFG1-DOTA-90Y (Kosmas et al., 1992) and 34 mCi of HMFG1-CITC-DTPA-90Y. A correlation between body surface and CITC-DTPA-90Y dose was found (Maraveyas et al., 1993). DOTA is potentially immunogenic in patients (Kosmas et al., 1992) as three out of six patients treated with HMG1-DOTA-90Y conjugate developed serum sickness reactions manifested as superficial and self-limiting skin rashes 10–12 days after treatment. It was also found that treated patients developed anti-DOTA (Kosmas et al., 1990) and anti-CITC-DTPA antibodies. All patients developed human antimouse antibodies as previously reported (Epenot et al., 1987; Stewart et al., 1989). The difference in toxicity and immunogenicity between DTPA and DOTA linkage between antibody and radionuclide as well as the HAMA levels are reported elsewhere (Kosmas et al., 1992; Maraveyas et al., 1993).

Survival

Figure 1 shows the survival data of the subgroup of 15 patients treated regarded as receiving adjuvant treatment and compares it with a similar group (70 patients) from the same centre (North Thames Ovarian Group). This group comprises of patients who presented with Stage IIb disease or worse and had no evidence of residual disease at laparoscopy following conventional treatment with surgery and chemotherapy. These data show a remarkable difference in survival between the group treated as adjuvant with antibody and the historical control from the North Thames Ovarian Group (Lambert et al., 1993). However, this is not the result.
of a randomised trial, and the patient numbers are small. Survival after antibody therapy of patients with bulky disease treated with radiolabelled antibody is: median survival of 11 months (range 2–31 months), with four patients still alive.

Discussion

The application of radiolabelled antibodies as specific cytotoxic drugs against cancer has many attractions including selectivity against tumour cells, irradiation of adjacent tumour cells, lack of major side effects and simplicity of radiolabelling and administration. Although tested extensively over the last decade, radiolabelled and other immunoconjugates have had only limited success as anticancer agents.

For the first time, this study demonstrates that radiolabelled antibodies used in an adjuvant setting may reduce the rate of recurrence from ovarian cancer and improve the long term survival. Although survival data from this study appear superior to previously reported studies (Neijt et al., 1984; Marsoni et al., 1990), the patient numbers are small and need to be substantiated by larger phase III randomised studies. Furthermore, because this was a phase I–II study, our cases included a mixture of stages from Ic-IV.

The mechanisms for the action of antibody therapy are not clear from this trial. The calculated doses of radiation delivered by the radioactive antibody are thought to be insufficient for a cytotoxic effect based on calculations using conventional dosimetry tables (Snyder et al., 1978) although more recent studies suggest that higher doses can be delivered (Larson et al., 1991). Unfortunately, there are no comprehensive data on the therapeutic efficacy of radioactive yttrium colloid alone given intraperitoneally after chemotherapy. An alternative possibility is that HMFG1 murine monoclonal antibody when administered intraperitoneally into humans, can cause a cascade of immunological reactions leading to humoral (Courtenay-Luck et al., 1988; Herlyn et al., 1991) and cellular (Kosmas et al., 1991) activation of the immune system with resultant antitumour effects. If this is the case of the observed prolongation of survival in patients with ovarian cancer in this study, then, ironically, the use of murine monoclonal antibodies may be more effective than the recently described chimeric (LoBuglio et al., 1989), humanised (Reichmann et al., 1988) or completely human (Borrebaeck et al., 1988) monoclonal antibodies.

In summary, this study provides encouragement to the concept of adjuvant therapy with monoclonal antibodies in patients with epithelial ovarian cancer who have no evidence of residual disease after initial surgery and chemotherapy.

We are grateful to the following: D. Allen, R. Biruls, C. Coulter, R. Chandler and J. Taylor-Papadimitriou.

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