Monoclonal antibodies in the treatment of ovarian cancer

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Summary

Monoclonal antibody application in ovarian cancer started eight years after the discovery of Köhler and Milstein, with the studies of Bast et al. which led to the introduction of CA 125 antigen estimation to everyday clinical routine. At present, monoclonal antibodies serve as a therapeutic tool for variable targets with the potential to be applied in multiple clinical situations. In the coming decade, the drug market is likely to be flooded with monoclonal antibodies. Most of the available monoclonal antibodies will be produced in bioreactors, using transgenic plants or transgenic animals. Apart from mouse antibodies, chimeric, humanised or human antibodies, oncology will certainly employ chimeric structures with antibody fragments built into the structures of receptors or growth factors. Irrespective of their origin, they will constitute an integral part of medical practice.

Key words: Monoclonal antibodies, Ovarian cancer.

Introduction

Since 1975 when Köhler and Milstein developed monoclonal antibodies, the range of their application in tumour diagnosis has been increasing: at present they are used for histopathological studies (immunohistochemistry) to estimate levels of tumour markers and for diagnostic imaging (immunotargeting) [1, 2]. In 1997 monoclonal antibodies were introduced for the treatment of tumours (rituximab). In the management of ovarian cancer monoclonal antibodies have not yet moved beyond the stage of clinical trials. Nevertheless, some of the studies have reached Stage III of trials and in the coming decade this form of treatment will also include ovarian cancer cases.

Commercially available monoclonal antibodies

At present, 11 monoclonal antibodies are available on the drug market. The first one, marketed in 1986, is the mouse monoclonal antibody which is used as an immunosuppressive drug in transplantology (Muromonab-CD3). Out of the five oncologically relevant monoclonal antibodies put on the market since 1997, four are applied in haematological oncology and only one in solid tumours (trastuzumab-Herceptin).

At the same time, a growing tendency has been observed to register new drugs, the monoclonal antibodies: between 1986 and 1996 two such drugs were approved while within the following five years (1997-2002) eight monoclonal antibody drugs came on the market. If this trend continues, 10-12 new drugs based on mo-

Type	Name	Product	Indication	Marketer	Approved
Chimeric	Rituximab	Rituxan	Non-Hodgkin's lymhoma	Genentech IDEC Pharmaceuticals	November 1997
CDR-grafted	Trastuzumab	Herceptin	Metastatic breast cancer	Genentech	September 1998
CDR-grafted	Gemtuzumab, Ozogamicin	Mylotarg	Acute myeloid leukemia	American Home Products WYETH	May 2000
CDR-grafted	Alemtuzumab	Campath	Chronic lymphocytic leukemia	Millennium ILEX	July 2001
Mouse antibody CD 20+	Ibritumomab Tiuxetan	Zevalin	Hodgkin's lymphoma	IDEC Schering AG	February 2002

noclonal antibodies can be expected to appear within the next 2.5 years. Except for the first of the drugs, Muromonab-CD3, all the other monoclonal antibodies available on the market at present represent already modified or chimeric antibodies (containing in their structure around 33% of a mouse antibody) or humanised antibodies (CDR-grafted, containing 5% to 10% of a mouse antibody structure). Fully human monoclonal antibodies (UltiMAb human antibody), produced by MEDAREX, are at the testing stage [3-6].

Will the new drugs include monoclonal antibodies applicable in the treatment of ovarian cancer?

Most probably yes. On analysis of the Medline data base using the key words: monoclonal antibody, monoclonal antibody and cancer, monoclonal antibody and ovarian cancer, and monoclonal antibody and ovarian cancer and therapy (in any place of the record), the number of publications on tumours linked to the key words monoclonal antibody has been decreasing steadily since the years 1993-1998. Also, the number of publications with the key words ovarian cancer and therapy of ovarian cancer has dropped. In contrast, the proportion of papers linked to tumours and monoclonal antibodies continues to grow (in 1999-2001 it was about 20% of all publications and in the first six months of 2002 - 22% of all publications). Similarly, the database of the US National Cancer Institute contains 7.7% of ongoing trials on therapy of ovarian cancer which involve the application of monoclonal antibodies as compared to 5.2% of trials already completed. The table below presents data from investigators and producers on the number of application trials.

Status of trial		Completed	Open/Active
Type of cancer	Ovarian epithelial cancer		
Type of trial	Treatment	686	78
Modality	Antibody therapy	36	6
%		5.2	7.7

The first studies, related to a respective type of ovarian cancer treatment, came from the mid-eighties [7, 8]. Monoclonal antibody was used as a selective carrier, delivering a radioactive isotope. In subsequent years it was used as a carrier of radioisotopes, toxins and cytostatic agents in a manner highly target-specific and thus reducing the toxic effects on the irrelevant tissues. In the last 15 years, the target epitopes have included CA 125, PEM, CEA, mesothelin, TAG-72, Lewis Y, HER 2/neu, VEGF, placental alkaline phosphatase and CD3 antigen of T lymphocytes [9-11]. The antibodies were used to deliver radioisotopes including yttrium (Y^{90}), lutetium (Lu^{177}), iodine (I^{131}) and (I^{125}) [12, 13], rhenium (Re^{186}), cytostatic drugs like cisplatin, anthracyclines, calicheamicin, vinca alkaloids, paclitaxel, as well as toxins such as *Pseudomonas* exotoxin A and *Pseudomonas* exotoxin 38 [14-18].

Another way of taking advantage of monoclonal antibodies involves using them to activate cell-mediated and humoral immune mechanisms by triggering cytotoxic T lymphocytes and inducing antibody-mediated cytotoxicity [19], or by stimulating anti-idiotypic antibody production (Ab-2 antibody) [20-22].

In recent years, treatment for ovarian and breast cancer has benefitted from the introduction of trastuzumab (Herceptin), which modifies the action of the membrane receptor, HER-2/*neu* (at the stage of testing), and bevacizumab, which modifies bioavailability of VEGF. In view of the specificity of ovarian cancer, the drugs can be administered either systemically by intravenous infusion or intraperitoneally, which some authors link to lower general toxicity.

Historically, the first attempts to apply monoclonal antibodies in the treatment of ovarian cancer involved paliative therapy of ascites and therapy of secondary or tertiary processes in cases of relapse or persisting disease. At present, a number of trials and studies are related to the treatment of microscopic disease detected during second-look procedures, to the treatment of patients with biochemical relapse (increased levels of CA 125 with no other signs of disease), and also as a safety measure for patients in complete clinical remission.

Undesirable activities of monoclonal antibodies

Application of monoclonal antibodies in the treatment of ovarian cancer may be complicated by undesirable side-effects. Myelotoxicity, hepatotoxicity, nausea and vomiting, neurotoxicity and fever (following application of toxins) are most frequently observed [15, 23, 24]. Intraperitoneal therapy can be complicated by episodes linked to the administrative procedure (complications of laparoscopy and catheter insertion) but episodes of intestinal necrosis have also been described as a direct consequence of radioisotope action [25]. When mouse antibodies are applied, almost all patients (HAMA-positive) report complaints linked to the development of an immune reaction, the flu-like syndrome. The reaction neutralises the administered antibodies and thus affects their half-life [26, 27]. Intensity of the reaction has been linked to the results of treatment [28].

Present status and results of trials on monoclonal antibodies in the treatment of ovarian cancer

The US National Cancer Institute database lists 36 completed studies on the effects of treating ovarian cancer using monoclonal antibodies at all stages of treatment: 23 Stage I trials, seven Stage I/II trials, five Stage II trials and one Stage III trial. Among the completed studies the most significant seem to be Stage II trials conducted by AltaRex Corp., Waltham, MA. The studies were conducted on 500 patients in six procedures, using OvaRex monoclonal antibody (B43.13) directed against CA 125 [3]. At present, the company offers OvaRex oregovomab (B43.13) and BrevaRex® Mab (targeting tumours with MUC1 expression) and AR54 Mab (targeting tumours with expression of TAG72 antigen). OvaRex (B43.13) is a mouse antibody with a high affinity to CA 125 antigen. The company suggests the application of the agent has immunotherapeutic effects, inducing or augmenting body reactions.

The most important research program at AltaRex examined the effects of the administered antibody as a stabilising treatment following complete recovery. The study was performed on 345 patients. The investigations were supplemented by five studies examining the effects of administering B43.13 antibody in patients with elevated CA 125 levels with no other signs of disease and in patients with relapse [29, 30]. Current analysis following inclusion of 75% of the planned patients indicates that application of OvaRex (B43.13) antibody

- acted as a stabilising measure by decreasing frequency of relapses in the first six months (analysis in the group of 252 patients: 79% vs 39% patients free of relapse);
- significantly prolonged the time to disease relapse (from 6 to 8 months) and reduced frequency of relapses by 19-29% as compared to the placebo group;
- acted through humoral immune mechanisms (HAMA, Ab-2) and cell-mediated immune mechanisms (antibody-dependent cytotoxicity);
- produced different results in patients with elevated levels of CA 125 (the so-called biochemical relapse) in two studies performed in the USA and Canada, which according to the investigators reflected unbalanced groups in the Canadian study with respect to unfavourable prognostic factors;
- demonstrated an extremely favourable safety profile and did not decrease quality of patients' life;
- showed significant differences in time to disease relapse and in survival rate ($p < 0.0001$ and $p = 0.008$, respectively) in patients with relapse after chemotherapy (results of non-randomised tests).

At present, under the supervision of the US National Cancer Institute, six trials are under way which are related to the therapy of ovarian cancer using monoclonal antibodies:

1. Phase I study of interleukin-12, paclitaxel and trastuzumab (herceptin) in patients with HER-2/*neu* overexpressing malignancies;
2. Phase I study of LMB-9 immunotoxin in patients with advanced colon, breast, non-small cell lung, bladder, pancreas or ovarian cancer;
3. Phase I study of SS1 (dsFv)-PE38 immunotoxin in patients with advanced malignancies that express mesothelin (Neopharm study)
4. Phase I study of yttrium, Y^{90}, monoclonal antibody MN-14 in patients with chemotherapy-resistant or refractory-advanced ovarian epithelial cancer;
5. Phase II study of bevacizumab in patients with persistent or recurrent ovarian epithelial or primary peritoneal cancer (GOG study);

6. Phase III randomised study of yttrium, Y90-labelled monoclonal antibody, HMFG1 vs standard therapy for patients with ovarian epithelial carcinoma in remission following debulking surgery and platinum-based chemotherapy (Antisoma study).

Most of these studies involve Stage I trials on small groups of patients. The only phase III trial is a study by the British pharmaceutical company Antisoma of yttrium, Y^{90}-labelled monoclonal antibody, HMFG1 vs standard therapy in patients with ovarian epithelial carcinoma in remission following debulking surgery and platinum-based chemotherapy termed SMART (study of monoclonal antibody radioimmuno-therapy). The employed antibody is pemtumomab (formerly known as theragyn).

Pemtumomab comprises a murine monoclonal antibody capable of conjugation to the radioisotope, yttrium-90. The antibody is specific for PEM, a marker overexpressed on the surface of epithelial tumour cells, including ovarian, gastric, pancreatic, colorectal, breast and lung tumour cells. This product was originally developed by the Imperial Cancer Research Fund, whose scientists carried out a long-term phase II study treating women with ovarian cancer, many with advanced stage disease. The study identified a subgroup of 21 women out of 52 participants who were in remission at the time of treatment and who responded well [31]. The company continues to follow the progress of these women. As of March 2000, 66% of the pentumomab-treated women, with a median follow-up in excess of eight years, were still alive.

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Antisoma is developing pemtumomab as an additional treatment for ovarian cancer following initial surgery and chemotherapy. Although technically these women may be in remission, with no detectable disease, statistics suggest that a high proportion may relapse. Treatment with a single intraperitoneal dose of pemtumomab is thought to target and destroy any target cells remaining after surgery and chemotherapy, thus preventing or delaying relapse.

The company is now conducting a multi-centre, randomised prospective Phase III study in monoclonal antibody radioimmunotherapy (SMART). The study is designed to demonstrate the safety profile and the potential survival advantage of pemtumomab for treated women, and to provide data required for its registration in the US and Europe. The initial target of recruiting 300 patients into the SMART study has been exceeded. In June 2001, the US Food and Drug Administration (FDA) recommended that the company should increase the statistical weight of the study by increasing the volume of required data. As a consequence, an additional 120 patients will be recruited over the next year. The primary aim is survival, with secondary goals measuring time to relapse, quality of life, length and frequency of hospital stays, adverse side-effects, etc. The study is being conducted in over 50 centres in North America, Europe and Australia.

An independent committee set up to monitor safety and other data in the SMART study has indicated that overall mortality in the studied population (i.e. all treated and control patients) is lower than expected at this stage of the study. Taken together with the FDA requirement for additional data, the projected date for application filing is unlikely to be before 2004.

Within the SMART study, it is now planned, subject to agreement with the regulatory authorities, that an interim analysis of its clinical data will be conducted after 75% of the agreed number of events has been reached, i.e., 87 deaths. The projected date of the interim analysis is likely to be approximately 12 months before the final analysis, so it is unlikely to be earlier than 2003.

Pemtumomab has been designated as an "orphan" medicine in both the US and the European Community, providing for seven and ten years' market exclusivity, respectively, once the marketing authorisation application is approved. Such legislation is intended to encourage the development of medicinal products for the treatment of rare or life-threatening diseases that might otherwise be commercially unavailable.

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