Recent Advances in Obstetrics & Gynaecology



Edited by
William Ledger • Justin Clark

Contents

Preface		**v**
Chapter 1	**Use of aortic balloon in massive postpartum haemorrhage** *Roberto Brunelli*	**1**
Chapter 2	**Fetal fibronectin and cervical ultrasound in prediction of preterm labour** *Sarah J Stock, Jane E Norman*	**11**
Chapter 3	**Medical management of endometriosis** *Arne Vanhie, Carla Tomassetti, Christel Meuleman, Thomas D'Hooghe*	**23**
Chapter 4	**Current state of antibody-based immunotherapy for ovarian cancer** *André Fedier, Brian WC Tse, Rosanna Zanetti Dällenbach, Viola A Heinzelmann-Schwarz*	**33**
Chapter 5	**The obese woman in late pregnancy and labour** *Amy O'Higgins, Michael J Turner*	**47**
Chapter 6	**First-trimester identification of risk of pre-eclampsia** *Lucy C Chappell, Shakila Thangaratinam, Jenny Myers*	**57**
Chapter 7	**Selective progesterone receptor modulators in gynaecology** *Vikram Sinai Talaulikar, Isaac Manyonda*	**67**
Chapter 8	**Minimising complications associated with caesarean section** *Malcolm Griffiths*	**79**

Chapter 9	**Changing practices in the management of first-trimester miscarriage** *Maya Al-Memar, Shyamaly D Sur*	93
Chapter 10	**The future of cervical screening** *Nirmala Rai, David Luesley*	107
Chapter 11	**Domestic violence and its relevance in obstetrics and gynaecology** *Tonye Wokoma, Stephen Lindow*	119
Chapter 12	**Pregnancy after assisted reproductive technology** *Jinny Yuting Foo, William Ledger, Michael Chapman*	127
Chapter 13	**Induction of labour: who, when, how and where?** *Kelly Mast, Mieke LG Ten Eikelder, Kitty WM Bloemenkamp, Josje Langenveld, Ben Willem J Mol*	135
Index		149

Chapter 4

Current state of antibody-based immunotherapy for ovarian cancer

André Fedier, Brian WC Tse, Rosanna Zanetti Dällenbach, Viola A Heinzelmann-Schwarz

SUMMARY

Ovarian cancer remains the gynaecological cancer with the highest mortality rate, despite improvement in outcomes with cytoreductive surgery and platinum-based chemotherapy. New chemotherapy drugs and particularly the alteration of the delivery cycles have increased the time over which this disease is controllable. However, novel therapies that can be integrated into existing treatment regimens are urgently needed. Immunotherapy is an alternative and rational therapeutic approach for ovarian cancer, based on evidence supporting a protective role of the immune system and on the clinical success of immunotherapy in other malignancies. Whether immunotherapy will have a significant role in the future management of ovarian cancer remains to be seen, but research in this field is active. In this chapter, the recent clinical developments of selected ovarian cancer-related immunotherapies fulfilling the criteria that they (1) are antibody based, (2) target a distinct immunological pathway and (3) have reached the clinical trial stage are discussed (**Table 4.1**). A particular focus is on catumaxomab (anti-EpCAM x anti-CD3), abagovomab and oregovomab (anti-CA125), daclizumab (anti-CD25), ipilimumab (anti-CTLA-4), MXD-1105 (anti-PD-L1) and CVac (anti-mucin1). We will also provide our perspective on the future of immunotherapy for ovarian cancer and discuss how such immunotherapies may be best employed in treatment regimens. In addition, recent research will be demonstrated in an immunotherapy-related field on naturally occurring antiglycan antibodies which might exhibit further therapeutical opportunities and potential.

André Fedier PhD, Department of Biomedicine, University Hospital Basel, Basel, Switzerland

Brian WC Tse PhD, Australian Prostate Cancer Research Centre-Queensland, Queensland University of Technology, Brisbane, Australia

Rosanna Zanetti Dällenbach PhD, Gynaecological Cancer Center, Women's University Hospital, Basel, Switzerland

Viola A Heinzelmann-Schwarz MD, Department of Biomedicine, University Hospital Basel, Basel, Switzerland; Lowy Cancer Research Centre, University of New South Wales, Sydney, Australia; and Gynaecological Cancer Center, Women's University Hospital, Basel, Switzerland. Email: viola.heinzelmann@usb.ch (for correspondence)

JAYPEE BROTHERS

INTRODUCTION

Epithelial ovarian cancer is the fifth most common malignancy in women and the second leading cause of death due to gynaecological cancer worldwide [1]. The majority of patients are diagnosed at an advanced International Federation of Gynecology and Obstetrics (FIGO) stage due to limitation of screening and the nonspecific nature of symptoms. The 5-year survival rate for women with early pelvic disease is over 70% but less than 30% for those with advanced metastatic disease [2]. Epithelial ovarian carcinomas are histologically categorised into serous (75%), mucinous (10%), endometrioid (10%), clear cell (1%) and undifferentiated (1%) subtypes. Maximal cytoreductive surgery and chemotherapy (carboplatin and paclitaxel) remain the two mainstays of adjuvant therapy, but approximately 70% of patients with advanced disease will relapse despite response to initial treatments [3].

OVARIAN CANCER IMMUNOTHERAPY

Immunotherapy represents an alternative and rational approach for the treatment of cancer, including ovarian cancer. A major function of the immune system is to continually seek out and eliminate cancer cells as they arise in a process referred to as cancer immunosurveillance [4]. Immunosurveillance involves both innate and adaptive immune mechanisms which function complimentarily to promote tumour immunity. Key to the antitumour immune responses is that it can be induced by immunological agents.

Several lines of clinical evidence collectively suggest that the immune system is protective against ovarian cancers and therefore forms the basis of immunotherapy for this disease. This is shown by a number of studies including a representative immunohistochemical analysis (186 advanced-stage ovarian cancers) which showed that 54.8% contained CD3+ T cells and that the presence of intratumoral T cells was associated with a higher 5-year overall survival (OS) rate of patients; 38% for those positive for T cells and 4.5% for those negative for T cells. In addition, patients with tumours containing T cells had a longer progression-free survival (PFS); 22.4 months and 5.8 months respectively [6]. To date, a number of ovarian cancer-associated antigens have been identified, including cancer antigen 125 (CA125) [7], homeobox protein A7 (HOXA7) [8], the cancer/testis antigen NY-ESO-1 [9,10], human epidermal growth factor (HER)-2/neu [11] and recently the P1 antigen [12]. These represent potential targets for therapeutic antibodies in cellular- and/or humoral-mediated antitumour immune responses.

ANTIBODIES AS THERAPEUTIC AGENTS FOR CANCER

Antibodies are glycoproteins composed of two heavy chains and two light chains joined by disulphide bonds, with the antigen-binding site located at the C-terminus and the constant region at the N-terminus. They are excellent anticancer agents by virtue of their high specificity for antigen, stability and easy generation via bioengineering technology. Antibodies can potentially induce tumour cell apoptosis via a number of mechanisms including (1) complement-dependent cytotoxicity (CDC), (2) antibody-dependent cellular cytotoxicity (ADCC), (3) indirect induction of tumour cell death through modulation of antitumour immunity via blockade of immune checkpoint inhibitors and (4) limiting tumour growth by binding to growth receptors, preventing interactions with endogenous ligands and hence inhibiting downstream signalling events.

JAYPEE BROTHERS

Here we will introduce recent developments in various antibody-based immunotherapies undergoing clinical trials for ovarian cancer. In addition, we will also shed light on antiglycan antibodies, which are naturally occurring antibodies (NAbs) that recognise exclusively polysaccharide epitopes rather than peptide epitopes localised on proteins and lipid chains.

Catumaxomab

Catumaxomab (Removab) is a monoclonal bispecific antibody approved in 2009 in the European Union for the intraperitoneal treatment of patients with malignant ascites. The antibody has two different antigen-binding sites: one for human epithelial cell adhesion molecule EpCAM (via a heavy and light chain of a rat IgG2b antibody), a type I transmembrane glycoprotein frequently overexpressed in ovarian cancers associated with lower OS [13,14], making EpCAM an attractive target in cancer immunotherapies; and one for human CD3 (via a heavy and light chain of a mouse IgG2a). The rationale of using catumaxomab is to activate and recruit T cells to EpCAM-expressing tumours whilst simultaneously stimulating accessory cells via their Fcγ receptors. The result is tumour cell destruction by ADCC and/or T-cell-mediated cytotoxicity via perforin and granzyme B [15].

Over 90% of ovarian cancer patients have EpCAM overexpressed on tumour cells present in ascites [16]. A phase I/II clinical trial involving 23 ovarian cancer patients with recurrent ascites due to progressive chemoresistant disease showed that treatment with catumaxomab resulted in a highly significant and sustained reduction of ascites including reduced or absent EpCAM-positive tumour cells in the ascites [17]. A phase II/III clinical trial with 258 patients with recurrent chemoresistant adenocarcinoma (ovarian, gastric, breast, pancreas, colon, endometrial) presenting with ascites demonstrated a sevenfold prolongation of the time to the next paracentesis [18]. Catumaxomab, an antibody composed of chains of mouse and rat origin, is expected to induce human anti-mouse antibodies (HAMAs) when administered to patients. Catumaxomab did indeed produce greater clinical benefits in cancer patients who developed HAMAs (median puncture-free survival was 64 versus 30 days for HAMA-positive/-negative ovarian cancer responders) [19]. It is generally well tolerated with most common adverse events being reversible mild-to-moderate nausea and abdominal pain, and therefore it appears to be a promising immunotherapy for ovarian cancer and may be particularly useful for patients presenting with chemotherapy-resistant disease and recurrent ascites.

Abagovomab and oregovomab

Antibodies can function as antigens in the form of 'antiidiotypic antibodies'. Immunisation with a given antigen (x) results in the generation of anti-x antibodies, which can be referred to as Ab1 [20]. Neils Jerne proposed that these antibodies may themselves be immunogenic, and he defined the immunogenic determinants of the antibody as idiotopes. The idiotopes of Ab1 can function as antigen that evoke the generation of antibodies (antiidiotypic). Ab2 are antibodies that result from exposure to Ab1, some of which are antiidiotypic. Since idiotopes are concentrated in the highly variable region of the antigen-binding site, some Ab2 will have idiotopes that effectively mimic the three-dimensional structure of antigen x. Experimental evidence suggests that in some circumstances, exposure to Ab2 may provoke a more effective response than exposure to antigen. These antibodies, in turn, may

JAYPEE BROTHERS

Table 4.1 Clinical trials of selected antibody-based immunotherapies for ovarian cancer

Immunotherapies in phase I-III trials (ovarian cancer)

Drug	Proposed mode of action	Antibody	Target antigen	Phase	Indication	No. of patients	Clinical notes	Reference no.
Catumaxomab	Trifunctional bi-specific antibody	Nonhumanised chimeric rat IgG2b/ mouse IgG2a	EpCAM	I/II	Recurrent ascites due to progressive chemoresistance	23	Reduced ascites volume and number of EpCAM+ in ascites	17
				II/III	Malignant ascites secondary to epithelial adenocarcinomas	258 (129 ovarian)	Treatment associated with longer median puncture-free survival and median time to next paracentesis	18
Abagovomab	Anti-idiotypic vaccine	Murine IgG1k	CA-125	I	FIGO stages III and IV ovarian cancer	42	Increased number of CA-125-specific CD8+ T cells in some patients	26
				I	FIGO stages I-IV ovarian cancer	36	Increased number of CA-125-specific CD8+ T cells in some patients	62
				Ib/II	Ovarian, tubal and peritoneal cancers	119	68.1% patients developed Ab3 responses, correlating with longer overall survival	25
				III	Ovarian cancer	888	Results pending	27
Oregovomab	Activation of idiotypic network	Murine IgG1	CA-125	II	FIGO stages I-IV ovarian cancer	20	Increased T-cell responses to CA-125 and autologous tumour cells in some patients, correlating with longer survival	30
				II	Recurrent ovarian, tubal and peritoneal adenocarcinoma	13	No overt reduction in tumour burden	32
				Not specified	FIGO stages I-IV ovarian cancer	184	Development of anti-CA-125 antibody (Ab3) responses in some patients	29

EXPERT BROTHERS

Table 4.1 *continued*

Drug	Proposed mode of action	Antibody	Target antigen	Phase	Indication	No. of patients	Clinical notes	Reference no.
				Not specified	FIGO stages I-IV ovarian cancer	75	Development of Ab2 and Ab3 levels in some patients. Evidence that Ab3 mediates antibody-dependent cellular cytotoxicity in some patients.	31
				Not specified	FIGO stages I- to IV ovarian cancer	49	Development of Ab2 and Ab3 levels in some patients, correlating with survival advantage	28
				III	FIGO stages III and IV	375	Oregovomab as a monoimmunotherapy did not improve clinical outcomes	33
Daclizumab	Antiregulatory T cell	Humanised IgG1	CD25	Not specified	Not specified	Not specified	Results pending	35
Ontak	Antiregulatory T cell	N/A (fusion protein of IL-2 and diphtheria toxin)	CD25	I/II	Advanced cancer	4 (2 ovarian)	Treatment associated with reduction in regulatory T cell numbers. Significant drop in CA-125 levels in one patient	37,41
Ipilimumab	Activation of effector T cells	Human IgG1	CTLA-4	I	Pretreated advanced melanoma or ovarian cancer	9 (2 ovarian)	CA-125 level stabilisation (one patient) and reduction (one patient)	43
				I	FIGO stage IV ovarian cancer previously received GVAX	9	Antitumour activity in one patient	44
MDX-1105	Immune checkpoint-inhibitor	IgG4	PD-L1	I	Not specified	207 (17 ovarian)	One partial response, three stable disease	49
CVac	Adoptive transfer of vaccine-primed T cells	Autologous dendritic cell-derived Ab	Mucin1	II	Recurrent advanced ovarian cancer	6	Vaccine-induced restoration of antitumour immunity in two patients	52,53

Adapted from Tse et al (2014) [5]. FIGO, International Federation of Gynecology and Obstetrics.

JAYPEE BROTHERS

stimulate the production of Ab3, some of which target the idiotopes of Ab2, and bind to antigen x.

CA125 is a high molecular weight mucin-like glycoprotein overexpressed on the surface of ovarian cancer cells. It is also shed into the bloodstream and is currently the most widely used tumour marker for ovarian cancer. A high level of serum CA125 at ovarian cancer diagnosis frequently indicates widespread peritoneal dissemination, and a continual increase in its value generally indicates disease progression [21,7]. Although CA125 is in clinical use as a tumour marker, its biological function is still poorly understood: some studies suggest that it is involved in cell adhesion, migration, metastasis, invasion and may have immunosuppressive properties [22,23].

Abagovomab (ACA-126) is a murine IgG1k monoclonal antibody (Ab2) with its idiotope imitating CA125 and is currently being investigated as an antiidiotypic vaccine for ovarian cancer. A phase I trial (42 patients with chemotherapy-resistant ovarian cancers; 93% with FIGO stages III-IV; 67% serous histotype) showed that abagovomab induced Ab3 and HAMA responses in all patients, that five of five patients also had detectable CA125-specific interferon gamma (IFN-γ)-producing T cells post vaccination, whereas none were detectable in any subjects prior to treatment, and that abagovomab in 25 patients strongly increased serum levels of IFN-γ, indicative of the induction of Th1 immune responses [24]. A phase Ib/II clinical trial with 119 patients with CA125-positive ovarian, tubal or peritoneal cancers showed that 68.1% of patients who received abagovomab developed Ab3 responses and exhibited significantly longer OS (23.4 vs. 4 months) even when stratified for FIGO stage, type of first-line chemotherapy and the number of previous therapies [25]. The mechanism by which abagovomab exerts its antitumour effect is likely to be ADCC. Such promising data together with the generally well-tolerability of the drug resulted in the initiation of a randomised double-blind placebo-controlled phase III trial involving 888 patients with FIGO stage III/IV ovarian cancer known as the 'Monoclonal antibody Immunotherapy for Malignancies of Ovary by Subcutaneous Abagovomab' (MIMOSA) trial [26]. Whilst abagovomab was shown to be safe and induced measurable immune responses, the study concluded that when the antibody was employed as a maintenance therapy for patients with first remission, it did not prolong relapse-free and OS [27].

Oregovomab (B43.13, OvRex) is a murine monoclonal antibody of IgG1 subclass with high affinity for CA125 (K_D = 1.2 – 10^{10} M^{-1}). It was initially developed as a technetium 99c-labelled antibody for the immunoscintigraphic detection of recurrent ovarian cancer by virtue of its expression of CA125 [28]. However, some patients who received this tumour-imaging agent had an unexpected survival advantage, prompting investigations into the antibody's potential as a therapy for ovarian cancer. Oregovomab evokes anti-CA125 antibody production and elicits tumour-specific T-cell responses rather than directly inhibiting tumour growth or inducing CDC or ADCC by itself.

A trial with 184 patients with ovarian cancer (FIGO stages I-IV) showed that a single treatment of oregovomab caused a rapid reduction in serum levels of CA125 due to the formation of immune complexes, that 26 out of 60 (43%) patients had a greater than threefold increase in anti-CA125 antibody levels, that anti-CA125 antibody responders also had longer survival times compared with nonresponders (22.9 vs. 13.5 months) and that 53% of patients showed an increase in T-cell proliferation in response to CA125, all together suggesting that the generation of humoral and cellular anti-CA125 responses contributes to the clinical benefits of oregovomab treatment [29]. Similarly, a phase II trial with 20 patients with platinum-resistant recurrent ovarian cancer (FIGO stages I-IV)

JAYPEE BROTHERS

demonstrated an oregovomab-increased T-cell response to CA125 in 39% of patients and to autologous tumour cells in 63%, both associated with longer survival [30]. In another trial with 75 patients with ovarian cancer (FIGO stages I-IV), oregovomab treatment (1-10 infusions) resulted in Ab2 antibody development in 64% and in anti-CA125 antibody development in 24% of the patients [31]. In a retrospective analysis of a previous trial with 44 patients with recurrent ovarian cancer (majority being FIGO stages III-IV), treatment with oregovomab resulted in the development of HAMA in 27 out of 40 patients (67.5%), antiidiotypic antibodies (Ab2) in 76.7% of patients, an increase by more than threefold in the level of anti-CA125 antibodies in 28% of patients and the ability of patients to generate these idiotypic network-related antibodies also correlated with a survival advantage [28]. Unfortunately, such promising clinical benefits of oregovomab were not confirmed in other studies. Although immune responses were observed, no overt tumour burden reduction was observed with oregovomab [32], clinical outcomes were similar to those given placebo [33], and more vigorous immune response were observed with carboplatin-paclitaxel administered in combination with oregovomab than observed with oregovomab in monoimmunotherapy [34].

Daclizumab and Ontak

Daclizumab (Zenapax) is a cell-depleting humanised IgG1 monoclonal antibody specific for CD25 and is currently being evaluated in clinical trials as an immunotherapy for a variety of cancers including ovarian cancer [35]. CD25 is expressed on regulatory T cells and on activated effector T cells. CD25+T cells were reported to be abundant in malignant ascites from previously untreated ovarian cancer patients compared to nonmalignant ascites and were also more abundant in FIGO stages III–IV ovarian cancers than in stages I–II tumours [36]. Moreover, higher tumour infiltration of regulatory T cells correlated with shorter patient survival [37,38], suggesting that regulatory T cells may facilitate ovarian cancer progression. Therefore, strategies which block or transiently deplete these cells may prove useful in treating cancer patients, a concept supported by animal studies whereby systemic removal of CD25+ cells with a cell-depleting monoclonal antibody can elicit potent and durable antitumour responses [39,40]. Whilst awaiting the results from clinical trials of daclizumab in ovarian cancer, data from clinical trials of Ontak, another form of CD25-targeted therapy, are encouraging.

Ontak (denileukin diftitox) is an engineered protein combining IL-2 with diphtheria toxin causing apoptosis of CD25+ cells. It is Food and Drug Administration (FDA) approved for the treatment of cutaneous T-cell leukaemia and currently being investigated as a therapy for other cancer types including metastatic ovarian cancer. In a phase I/II clinical trial with seven patients with advanced adenocarcinomas, including ovarian cancer, Ontak treatment was generally well tolerated, reduced CD3+CD4+CD25+ cells in peripheral blood, increased the number of circulating IFN-γ-producing T cells [36] and significantly reduced blood CA125 level in one patient with FIGO stage IV ovarian cancer associated with the resolution of all lymph node, visceral and bone metastases [41].

Ipilimumab

Ipilimumab (MDX-CTLA-4, Yervoy) is a fully human IgG1 monoclonal antibody. Ipilimumab binds to and blocks the activity of cytotoxic T-lymphocyte-associated antigen 4, CTLA-4, a homologue of CD28 expressed on the surface of T cells upon activation and

JAYPEE BROTHERS

a key molecule in the downregulation of T-cell activity as a means to limit self-damage. In this sense, CTLA-4 functions as an immune-checkpoint receptor that mediates immune suppression. The use of therapeutic agents to block CTLA-4 function prevents immune inactivation and therefore is a rational approach to evoke effective antitumour immune responses. Ipilimumab was recently approved by the FDA for the treatment of advanced melanoma [42], but a few studies have been conducted in ovarian cancer. One of those, a phase I/II trial with 11 patients with FIGO stage IV ovarian cancers who had previously either received chemotherapy or GVAX [a vaccine product composed of autologous, irradiated tumour cells engineered to secrete the immune stimulatory cytokine, granulocyte macrophage colony-stimulating factor (GM-CSF)] showed that ipilimumab was generally well tolerated with the exception of some grade 3 inflammatory toxicities, and exhibited significant antitumour effects in one ovarian cancer patient who showed a dramatic fall of serum CA125 levels during treatment with a substantial regression of a large hepatic metastasis, mesenteric lymph nodes and an omental cake, resulting in pain and ascites reduction. Four other patients had stabilisation of disease as assessed by blood CA125 levels and imaging [43,44].

CURRENT STATE OF IMMUNOTHERAPY IN OVARIAN CANCER

It is still unclear whether immunotherapy, both vaccine- and antibody-based, has the potential to be incorporated into treatment regimens against ovarian cancer. For the former, a study with 12 patients with relapsed epithelial ovarian cancer has recently been performed to increase the NY-ESO-1 vaccine efficacy [45]. This phase I dose-escalation trial of decitabine (a DNA methyltransferase inhibitor), as an addition to NY-ESO-1 vaccine and doxorubicin liposome (doxorubicin) chemotherapy, showed increased NY-ESO-1 serum antibodies and T-cell responses in the majority of patients (disease stabilisation or partial clinical response in 6 out of 10 evaluable patients), warranting further evaluation of similar combinatorial chemoimmunotherapy regimens in epithelial ovarian cancer. For the latter, an increasing number of antibody-based immunotherapeutics have reached the clinical trial stage over the past decade. Whilst catumaxomab, abagovomab and oregovomab have already reached phase III, many other new antibody-based treatments have just entered phase I and II clinical trials. Catumaxomab particularly shows promise and was recently approved by the European Community for the treatment of malignant ascites. Results from larger trials of this antibody are greatly anticipated. Abagovomab and oregovomab, both of which appeared promising based on early clinical trials, have been largely disappointing in recent phase III trials with no overt antitumour efficacy reported. In recent years, immune-checkpoint inhibitors such as ipilimumab, MDX-1105 and MDX-1106, have emerged as candidates for cancer immunotherapy but only a few small clinical trials for ovarian cancer have been conducted so far.

MDX-1105 and MDX-1106, contrary to ipilimumab, target the PD-1/PD-L1 axis. In contrast to CTLA-4, the main function of which is to regulate the activation of naive T cells, PD-1 (programmed cell death 1) predominantly restrains the activity of effector T cells within peripheral tissues (e.g. sites of chronic inflammation, infection or cancer) to limit autoimmunity [46]. Interaction of PD-1 with its ligand, PD-1 ligand 1 (PD-L1), inhibits T-cell proliferation, survival and effector functions, induces apoptosis of antigen-specific T cells, promotes the conversion of CD4+ T cells to regulatory T cells and induces tumour

JAYPEE BROTHERS

resistance to cytotoxic T-cell killing [47]. Therefore, blockade of the PD-1/PD-L1 axis could potentially enhance the strength of antitumour immunity, with the goal to produce durable clinical responses. In ovarian cancer, PD-L1 expression has been shown to be an independent factor for poor prognosis [48]. The results indicate that the PD-1/PD-L1 axis is involved in immune evasion in ovarian cancer, and that blockade of this immune checkpoint pathway may unleash the potential of antitumour immunity to mediate tumour regression.

MDX-1105 (BMS-936559) is a fully human IgG4 monoclonal antibody with high affinity for PD-L1. It inhibits the binding of PD-L1 to PD-1, and is a noncell-depleting antibody. A phase I clinical trial with 207 patients with a variety of cancer types reported encouraging results [49]. In the ovarian cancer arm, 1 of 17 patients (6%) had a partial response (defined as at least a 30% decrease in the sum of the largest diameter of target lesions) and 3 (18%) had stable disease lasting over 24 weeks.

MDX-1106 (BMS-936558) is also a fully human IgG4-blocking monoclonal antibody that is directed against PD-1. To date, there have been two phase I clinical trials which investigated the safety and antitumour activity of this antibody, although neither recruited ovarian cancer patients [50,51]. However, results from other cancer types are showing promise and inclusion of ovarian cancer patients in future trials is warranted.

A promising advance can be highlighted by a recent report of George Coukos and coworkers [52]. They demonstrated that an autologous dendritic cell-derived antibody directed against mucin1 (CVac), a glycoprotein highly overexpressed in ovarian cancer, triggered an antitumour response in ovarian cancer patients who were unresponsive to existing treatments. This two-step personalised immunotherapy treatment showed a vaccine-induced restoration of antitumour immunity in these patients with an improved median PFS at the time of the second remission. A respective phase II clinical trial (CAN-003) has just been completed and was presented at the American Society of Clinical Oncology-Meeting in 2014 [53]. This study was the first immunotherapy trial showing a positive survival result for ovarian cancer patients by extending their PFS from the treatment with CVac. Mucin1 is an ideal target for immunotherapy as it is a glycoprotein which is overexpressed in many adenocarcinomas including ovarian cancers (83%). Patients receiving CVac showed no benefit in PFS at the time of their first relapse ($P = 0.69$). However, an improved PFS was seen at the time of their second relapse with a median PFS without immunotherapy of 4.9 months compared to over 12.9 months with immunotherapy (endpoint not yet reached); $P = 0.04$; hazard ratio 0.329. These results suggest that survival effects from immunotherapy may take longer than previously estimated and caution has to be taken to downplay overoptimistic interpretation of early trial results.

CRITICAL CONSIDERATIONS OF IMMUNOTHERAPY AND LESSONS LEARNT

For the field of immunotherapy research to move forward, it is important to consider the limiting factors of clinical trials in order to improve the design of future studies.

One limitation common to almost all cancer clinical trials is that the patients already have advanced disease. This is a major issue especially for immunotherapy because the ability to initiate an immune response, or its magnitude, is limited by the extent of disease burden, the suppressive effect of the tumour microenvironment and the multiple layers of immunological tolerance mechanisms (e.g. regulatory T cells) which keep the immune

JAYPEE BROTHERS

response in check. As a consequence, immune-based therapies are more likely to be effective in patients with low volume disease such as earlier stage cancers or immediately after cytoreductive treatment with minimal residual disease.

A consideration not to be overlooked is whether immunotherapies are offered as monotherapy or as an adjunct therapy. Realistically, if immunotherapy is to be applied to ovarian cancer treatment regimens in the short-to-medium term, it would be as an adjunct therapy rather than as a frontline monotherapy. Future clinical trials should investigate the synergistic potential of immune-modulating agents with established chemotherapies. Indeed, oregovomab was recently investigated as a combination therapy with standard carboplatin–paclitaxel in a phase II clinical trial, and stronger immune responses were measured than those reported in a previous monoimmunotherapy protocol [34]. Chemoimmunotherapy is appealing not only because chemotherapies directly induce apoptosis of tumour cells and result in the release of antigen to drive immune responses, but they often also disrupt essential immune regulatory mechanisms that limit the development of immunity, an increasingly appreciated attribute [54]. An ideal combination of chemoimmunotherapy would be one where both agents have minimal overlapping toxicities, work via independent mechanisms but have additive or synergistic antitumour effects. A successful example of this approach is the combination of fludarabine, cyclophosphamide and rituximab for chronic lymphocytic leukaemia. The addition of rituximab to the chemotherapies increased the rate of complete remission and OS [55]. However, it is critical to optimise the dosage, sequence and timing of administering each drug as all these parameters could impact on the outcome.

Another point to consider in the design of future clinical trials is to acknowledge that ovarian cancer is a heterogeneous disease with four major histological subtypes, each of which has distinct genetic profiles which may affect the ability and/or magnitude of immune responses evoked by an immunotherapy. The heterogeneity of ovarian cancer can be further highlighted by differences in the antiglycan antibody profiles in serum and ascites of patients with various histotypes (discussed in more detail below). Therefore, it may be necessary to conduct clinical trials on more homogenous populations; e.g. serous cancer patients only, to have greater power to detect potential clinical efficacy. Pooling patients into a single cohort may reduce the sensitivity to detect clinical benefits to certain histotypes. The importance of stratifying treatment based on histotype is supported by recent evidence of contrasting clinical outcomes in mucinous and serous ovarian cancers when treated with platinum-based chemotherapy [56]; these two histotypes may be distinct entities, and investigations are underway to determine how each could be managed best.

Naturally occurring antiglycan antibodies: new players in ovarian cancer diagnosis and therapy?

NAbs are immunoglobulins predominantly of IgM class which are secreted by B1 B cells in the absence of external antigen stimulation. They play an important role in protection against infectious material, removal of cellular waste and in limiting chronic inflammation [57]. NAbs bind to oligosaccharides with low affinity and are oligoreactive. There is emerging evidence that these antibodies play an important role in cancer

JAYPEE BROTHERS

immunosurveillance. It was shown that tumour-specific NAbs exist in both healthy individuals and cancer patients, and can recognise and eliminate intact tumour cells via CDC [58].

Recently, our group reported an intriguing relationship between ovarian cancer, carbohydrate antigens and antiglycan antibodies. Using a printed glycan array, we demonstrated that ovarian cancer patients had significantly different levels of antibodies to a variety of glycans including several established tumour-associated carbohydrate antigens as compared to healthy women [59–61]. This was recently confirmed by our in-house developed suspension glycan array. In addition, it demonstrated that the ability of antiglycan antibodies to discriminate between the two groups was due to IgM rather than IgG in most cases and was also patient cohort independent [12]. The glycan with the most significant discriminatory ability was P1, a member of the P blood group antigens. P1 is covalently attached to ceramide to form a glycosphingolipid; glycosphingolipids are essential constituents of mammalian cell membranes. We recently reported that P1 is expressed on the surface of ovarian cancer cell lines as well as ovarian cancer tissue, and that it is functionally related to cell migration [12]. As such, P1 is a potential biomarker for ovarian cancer, and may be a rational target for immunotherapies.

An important lesson learnt in recent years is not to become overly excited with novel drugs that show particular promise in phase I and/or II clinical trials because quite often they fail to meet the high expectations in phase III studies. Although these results seem disappointing, it is important for research into immunotherapy for ovarian cancer, in combination with chemotherapy, to continue because there are glimpses of efficacy in some patients from initial studies. We need to think critically about the reasons for this, and design future clinical trials accordingly.

CONCLUSION

A wide range of immune-modulating approaches are currently being evaluated for the treatment of ovarian cancer. As the results of clinical trials of the discussed antibody-based immunotherapies are inconsistent, it is still too early to conclude if these drugs will be incorporated into treatment regimens against ovarian cancer. Furthermore, their true potential may lie within being strategically employed in chemoimmunotherapy regimens.

Key points for clinical practice

- Various forms of immunotherapy continue to be evaluated in clinical trials for ovarian cancer, especially within the context of advanced disease and/or relapse.
- It is currently too early to tell whether or not immunotherapy will be utilised in future treatment regimens for ovarian cancer, but research in this field is active.
- The optimal timing and scheduling of immunotherapy together with conventional therapies need to be established in future clinical trials.
- It is important to acknowledge that ovarian cancer is a heterogeneous disease, and therefore the different histotypes may require different treatment modalities. Antiglycan antibodies are NAbs and might be a new class of antibodies which could be used for immunotherapy.

JAYPEE BROTHERS

REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69–90.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62:10–29.
3. Ushijima K. Treatment for recurrent ovarian cancer-at first relapse. J Oncol 2010; 2010:497429.
4. Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. Adv Immunol 2006; 90:1–50.
5. Tse BW, Collins A, Oehler MK, et al. Antibody-based immunotherapy for ovarian cancer: where are we at? Ann Oncol 2014; 25:322–331.
6. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 2003; 348:203–213.
7. Bast RC, Jr. CA 125 and the detection of recurrent ovarian cancer: a reasonably accurate biomarker for a difficult disease. Cancer 2010; 116:2850–2853.
8. Naora H, Montz FJ, Chai CY, et al. Aberrant expression of homeobox gene HOXA7 is associated with mullerian-like differentiation of epithelial ovarian tumors and the generation of a specific autologous antibody response. Proc Natl Acad Sci U S A 2001; 98:15209–15214.
9. Odunsi K, Jungbluth AA, Stockert E, et al. NY-ESO-1 and LAGE-1 cancer-testis antigens are potential targets for immunotherapy in epithelial ovarian cancer. Cancer Res 2003; 63:6076–6083.
10. Odunsi K, Matsuzaki J, Karbach J, et al. Efficacy of vaccination with recombinant vaccinia and fowlpox vectors expressing NY-ESO-1 antigen in ovarian cancer and melanoma patients. Proc Natl Acad Sci U S A 2012; 109:5797–5802.
11. Camilleri-Broet S, Hardy-Bessard AC, Le Tourneau A, et al. HER-2 overexpression is an independent marker of poor prognosis of advanced primary ovarian carcinoma: a multicenter study of the GINECO group. Ann Oncol 2004; 15:104–112.
12. Jacob F, Anugraham M, Pochechueva T, et al. The glycosphingolipid P1 is an ovarian cancer-associated carbohydrate antigen involved in migration. Br J Cancer 2014; 111:1634–1645.
13. Spizzo G, Went P, Dirnhofer S, et al. Overexpression of epithelial cell adhesion molecule (Ep-CAM) is an independent prognostic marker for reduced survival of patients with epithelial ovarian cancer. Gynecol Oncol 2006; 103:483–488.
14. Heinzelmann-Schwarz VA, Gardiner-Garden M, Henshall SM, et al. Overexpression of the cell adhesion molecules DDR1, Claudin 3, and Ep-CAM in metaplastic ovarian epithelium and ovarian cancer. Clin Cancer Res 2004; 10:4427–4436.
15. Seimetz D, Lindhofer H, Bokemeyer C. Development and approval of the trifunctional antibody catumaxomab (anti-EpCAM x anti-CD3) as a targeted cancer immunotherapy. Cancer Treat Rev 2010; 36:458–467.
16. Diaz-Arias AA, Loy TS, Bickel JT, et al. Utility of BER-EP4 in the diagnosis of adenocarcinoma in effusions: an immunocytochemical study of 232 cases. Diagn Cytopathol 1993; 9:516–521.
17. Burges A, Wimberger P, Kumper C, et al. Effective relief of malignant ascites in patients with advanced ovarian cancer by a trifunctional anti-EpCAM x anti-CD3 antibody: a phase I/II study. Clin Cancer Res 2007; 13:3899–3905.
18. Heiss MM, Murawa P, Koralewski P, et al. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: results of a prospective randomized phase II/III trial. Int J Cancer 2010; 127:2209–2221.
19. Ott MG, Marme F, Moldenhauer G, et al. Humoral response to catumaxomab correlates with clinical outcome: results of the pivotal phase II/III study in patients with malignant ascites. Int J Cancer 2012; 130:2195–2203.
20. Jerne NK. Clonal selection in a lymphocyte network. Soc Gen Physiol Ser 1974; 29:39–48.
21. Rustin GJ, Marples M, Nelstrop AE, et al. Use of CA-125 to define progression of ovarian cancer in patients with persistently elevated levels. J Clin Oncol 2001; 19:4054–4057.
22. Gubbels JA, Belisle J, Onda M, et al. Mesothelin-MUC16 binding is a high affinity, N-glycan dependent interaction that facilitates peritoneal metastasis of ovarian tumors. Mol Cancer 2006; 5:50.
23. Patankar MS, Jing Y, Morrison JC, et al. Potent suppression of natural killer cell response mediated by the ovarian tumor marker CA125. Gynecol Oncol 2005; 99:704–713.
24. Sabbatini P, Dupont J, Aghajanian C, et al. Phase I study of abagovomab in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer. Clin Cancer Res 2006; 12:5503–5510.

KARGER BROTHERS

25. Reinartz S, Kohler S, Schlebusch H, et al. Vaccination of patients with advanced ovarian carcinoma with the anti-idiotype ACA125: immunological response and survival (phase Ib/II). Clin Cancer Res 2004; 10:1580–1587.
26. Sabbatini P, Berek JS, Casada A, et al. Abagovomab maintenance therapy in patients with epithelial ovarian cancer after complete response (CR) post-first-line chemotherapy (FLCT): preliminary results of the randomized, double-blind, placebo-controlled, multicenter MIMOSA trial. J Clin Oncol 2010; 28;15 Suppl:5036.
27. Sabbatini P, Harter P, Scambia G, et al. Abagovomab as maintenance therapy in patients with epithelial ovarian cancer: a phase III trial of the AGO OVAR, COGI, GINECO, and GEICO––the MIMOSA study. J Clin Oncol 2013; 31:1554–1561.
28. Mobus VJ, Baum RP, Bolle M, et al. Immune responses to murine monoclonal antibody-B43.13 correlate with prolonged survival of women with recurrent ovarian cancer. Am J Obstet Gynecol 2003; 189:28–36.
29. Noujaim AA, Schultes BC, Baum RP, et al. Induction of CA125-specific B and T cell responses in patients injected with MAb-B43.13––evidence for antibody-mediated antigen-processing and presentation of CA125 in vivo. Cancer Biother Radiopharm 2001; 16:187–203.
30. Gordon AN, Schultes BC, Gallion H, et al. CA125- and tumor-specific T-cell responses correlate with prolonged survival in oregovomab-treated recurrent ovarian cancer patients. Gynecol Oncol 2004; 94:340–351.
31. Schultes BC, Baum RP, Niesen A, et al. Anti-idiotype induction therapy: anti-CA125 antibodies (Ab3) mediated tumor killing in patients treated with Ovarex mAb B43.13 (Ab1). Cancer Immunol Immunother 1998; 46:201–212.
32. Ehlen TG, Hoskins PJ, Miller D, et al. A pilot phase 2 study of oregovomab murine monoclonal antibody to CA125 as an immunotherapeutic agent for recurrent ovarian cancer. Int J Gynecol Cancer 2005; 15:1023–1034.
33. Berek J, Taylor P, McGuire W, et al. Oregovomab maintenance monoimmunotherapy does not improve outcomes in advanced ovarian cancer. J Clin Oncol 2009; 27:418–425.
34. Braly P, Nicodemus CF, Chu C, et al. The immune adjuvant properties of front-line carboplatin-paclitaxel: a randomized phase 2 study of alternative schedules of intravenous oregovomab chemoimmunotherapy in advanced ovarian cancer. J Immunother 2009; 32:54–65.
35. Vasievich EA, Huang L. The suppressive tumor microenvironment: a challenge in cancer immunotherapy. Mol Pharm 2011; 8:635-641.
36. Barnett B, Kryczek I, Cheng P, et al. Regulatory T cells in ovarian cancer: biology and therapeutic potential. Am J Reprod Immunol 2005; 54:369–377.
37. Barnett JC, Bean SM, Whitaker RS, et al. Ovarian cancer tumor infiltrating T-regulatory (T(reg)) cells are associated with a metastatic phenotype. Gynecol Oncol 2010; 116:556–562.
38. Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci U S A 2005; 102:18538–18543.
39. Shimizu J, Yamazaki S, Sakaguchi S. Induction of tumor immunity by removing CD25+CD4+ T cells: a common basis between tumor immunity and autoimmunity. J Immunol 1999; 163:5211–5218.
40. Tien AH, Xu L, Helgason CD. Altered immunity accompanies disease progression in a mouse model of prostate dysplasia. Cancer Res 2005; 65:2947–2955.
41. Barnett B, Kryczek I, Cheng P, et al. Regulatory T cells in ovarian cancer: biology and therapeutic potential. Am J Reprod Immunol 2005;54:369-377.
42. Sondak VK, Smalley KS, Kudchadkar R, et al. Ipilimumab. Nat Rev Drug Discov 2011; 10:411–412.
43. Hodi FS, Mihm MC, Soiffer RJ, et al. Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. Proc Natl Acad Sci U S A 2003; 100:4712–4717.
44. Hodi FS, Butler M, Oble DA, et al. Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients. Proc Natl Acad Sci U S A 2008; 105:3005–3010.
45. Odunsi K, Matsuzaki J, James SR, et al. Epigenetic potentiation of NY-ESO-1 vaccine therapy in human ovarian cancer. Cancer Immunol Res 2014; 2:37–49.
46. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12:252–264.

JAYPEE BROTHERS

47. Zitvogel L, Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. Oncoimmunology 2012; 1:1-3.
48. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci U S A 2007; 104:3360–3365.
49. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012; 366:2455–2465.
50. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010; 28:3167–3175.
51. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366:2443–2454.
52. Kandalaft LE, Powell DJ, Jr., Chiang CL, et al. Autologous lysate-pulsed dendritic cell vaccination followed by adoptive transfer of vaccine-primed ex vivo co-stimulated T cells in recurrent ovarian cancer. Oncoimmunology. 2013; 2:e22664.
53. Gray HJ, Gargosky SE, CAN-003 Study Team. Progression-free survival in ovarian cancer patients in second remission with mucin-1 autologous dendritic cell therapy. J Clin Oncol 2014; 32;15 Suppl:5504.
54. Emens LA. Chemotherapy and tumor immunity: an unexpected collaboration. Front Biosci 2008; 13:249–257.
55. Tam CS, Keating MJ. Chemoimmunotherapy of chronic lymphocytic leukemia. Nat Rev Clin Oncol 2010; 7:521–532.
56. Naik JD, Seligmann J, Perren TJ. Mucinous tumours of the ovary. J Clin Pathol 2012; 65:580–584.
57. Schwartz-Albiez R, Monteiro RC, Rodriguez M, et al. Natural antibodies, intravenous immunoglobulin and their role in autoimmunity, cancer and inflammation. Clin Exp Immunol 2009; 158 Suppl 1:43–50.
58. Brandlein S, Pohle T, Ruoff N, et al. Natural IgM antibodies and immunosurveillance mechanisms against epithelial cancer cells in humans. Cancer Res 2003; 63:7995–8005.
59. Jacob F, Goldstein DR, Bovin NV, et al. Serum antiglycan antibody detection of nonmucinous ovarian cancers by using a printed glycan array. Int J Cancer 2012; 130:138–146.
60. Pochechueva T, Jacob F, Fedier A, et al. Tumor-associated glycans and their role in gynecological cancers: accelerating translational research by novel high-throughput approaches. Metabolites 2012; 2:913–939.
61. Pochechueva T, Jacob F, Goldstein DR, et al. Comparison of printed glycan array, suspension array and ELISA in the detection of human anti-glycan antibodies. Glycoconj J 2011; 28:507–517.
62. Pfisterer J, du Bois A, Sehouli J, et al. The anti-idiotypic antibody abagovomab in patients with recurrent ovarian cancer. A phase I trial of the AGO-OVAR. Ann Oncol 2006; 17:1568–1577.

JAYPEE BROTHERS

Recent Advances in Obstetrics & Gynaecology 26

Recent Advances in Obstetrics & Gynaecology 26 is the ideal resource for keeping abreast of new developments in this fast-moving field. Written by expert authors and featuring topics such as first-trimester identification of risk of pre-eclampsia and the future of cervical screening, each chapter highlights the latest developments of relevance to clinical practice. This book is an invaluable update and revision tool for trainees preparing for postgraduate examinations.

- Practical and clinically relevant content, enhanced by *Key Points for Clinical Practice* at the end of each chapter
- Chapters focus on important recent developments in the field of obstetrics and gynaecology
- Effective revision tool for candidates sitting postgraduate obstetrics and gynaecology examinations

JP medical publishers

www.jpmedpub.com

ISBN 978-1-909836-26-6