Ovarian Cancer: the Prospect of Development of Vaccines Therapy

Samir A. Farghaly, M.D., PhD

Abstract — Ovarian cancer is the seventh most common cancer in women worldwide (18 most common cancer overall), with 239,000 new cases diagnosed in 2012. In the USA, estimated new cases of ovarian cancer in 2014: 21,980, and estimated deaths from ovarian cancer in 2014: 14,270. Ovarian cancer often has no symptoms at the early stages, so the disease is generally advanced when it is diagnosed. The 5-year survival rate (which compares the 5-year survival of people with the cancer to the survival of others at the same age who do not have cancer) ranges from approximately 30 to 50 per cent.

Keywords — Ovarian cancer; Ovarian cancer antigens; Adjuvant ovarian cancer therapy; ovarian cancer immunotherapy; Ovarian cancer vaccines.

Ovarian cancer is immunogenic, and the ability of the immune system to recognize ovarian cancer is associated with improved prognosis. T Cell infiltration in the ovarian cancers shown to improve prognosis in several studies. The first observation came about in 1982 (1). The presence of intratumoral T cells observed in several studies to be an independent prognostic factor for progression -free survival (PFS) and overall survival (OS) by multivariate analysis. Specifically cytotoxic CD8+ T-cells (2, 3, 4–8). Regulatory T cells, which can modulate immune responses and maintain tolerance to self-antigen, have been shown to predict poor survival in ovarian cancer (4,8). It was reported that over 60% of women diagnosed with ovarian cancer will have distant metastases however, response rates to initial chemotherapy and cytoreductive surgery can be 85% (9). Despite these initial responses, about two thirds of patients will recur and recurrence occurs even in patients who achieved complete remissions (10). Cure rates of this disease have changed little, despite advances in therapies, and most patients can expect a relapsing and remitting clinical course of resistance to chemotherapies. However, periods of remission could allow vaccines the necessary time in patients with low disease burdens to induce an effective antitumor response to prolong remissions and prevent recurrences. Modulating T-cells, observed to demonstrate responses in ovarian cancer patients. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) engagement of co stimulatory molecules can result in the arrest of T cell responses and impaired anti tumor response. Antibody blockage of CTLA-4 was used in pretreated ovarian cancer patients, who had received multiple chemotherapy agents, four of nine patients achieved biochemical and radiological response without significant toxicities (11,12). Programmed death 1 (PD-1) is a T-cell co inhibitory receptor. Antibody blockage of its ligand, PD-L1, has been studied in patients with advanced cancers, including ovarian cancer. Patients were treated with anti-PD-L1 antibody to block inhibitory signals on effector T cells. 18% of ovarian cancer patients were able to achieve stable disease for at least 6 months (13). This suggests that vaccines capable of generating focused immune responses specifically targeting tumor antigens may be more effective. Cancer vaccines have been evaluated using a number of platforms including peptides/protein or DNA in combination with adjuvant, anti-idiotypic vaccines, recombinant viruses or other microbes, tumor cells or tumor cell lysates, or the delivery of activated dendritic cells to patients. These strategies are currently being studied for ovarian cancer. Peptide have been investigated, as they allow the direct translation of an identified tumor associated antigen into a vaccine and measurement of immune responses. However, peptides and proteins are limited in eliciting a durable CD4 and CD8 responses alone. Peptide and protein based vaccine platforms are usually administered with an immune modulator or adjuvant because, as they are weakly immunogenic. In phase 1 trial of ovarian cancer patients using overlapping long peptides from a human tumor self-antigen, NY-ESO-1 with poly- ICLC adjuvant. The vaccine was well tolerated and able to induce both cellular, CD4+ and CD8+, and antibody responses in most of the vaccinated patients (25). Downregulation of surface MHC class I is thought to be a strategy of immune evasion in a number of human cancers. Selected peptides from candidate antigens: p53, SP17, survivin, WT1, and NY-ESO-1 has been studied as multi antigen vaccine (26). The authors observed, that 93.2% of the studied samples from primary ovarian cancer patients over expressed at least one of the candidate antigens. Over 70% of patients over expressed 2 or more of the candidate antigens. The authors also found that expression of MHC class I was present in over 78% of ovarian cancers tested. This suggests that a vaccine directing a cellular immune response against multiple target antigens may be beneficial in ovarian cancer. The ideal antigen for an ovarian cancer vaccine would be singularly expressed on tumor cells or tumor cell lysates, or the delivery of activated dendritic cells to patients. These strategies are currently being studied for ovarian cancer. Peptide have been investigated, as they allow the direct translation of an identified tumor associated antigen into a vaccine and measurement of immune responses. However, peptides and proteins are limited in eliciting a durable CD4 and CD8 responses alone. Peptide and protein based vaccine platforms are usually administered with an immune modulator or adjuvant because, as they are weakly immunogenic. In phase 1 trial of ovarian cancer patients using overlapping long peptides from a human tumor self-antigen, NY-ESO-1 with poly- ICLC adjuvant. The vaccine was well tolerated and able to induce both cellular, CD4+ and CD8+, and antibody responses in most of the vaccinated patients (25). 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anti tumor response, and be able to be expressed. The target ought be biologically viable in maintaining the malignant phenotype, so tumor cells cannot escape immune targeting. These are defined as tumor specific antigens. These antigens, are less immuno-genic. A number of candidate antigens including HER2/neu, p53, CA125, MUC1, CEA, folate receptor alpha, cancer testis antigens like NY-ESO-1 and insulin growth factor binding proteins have been studied as potential vaccine targets in ovarian cancer (14–24). Plasmid DNA vaccines have been investigated in several cancers. Its advantages are more stable, easy to manufacture, and can be given in a smaller volume than synthetic peptides. In addition, plasmids may be modified to encode non-self antigens to enhance immunogenicity. Viral and microbial vectors have also been explored as vehicles for cancer vaccines. Poxviral vectors, due to their large genome, can allow the insertion of multiple genes, which may include the target antigen or antigens and immunostimulatory factors. In a trial conducted at the National Cancer Institute (NIH), USA, 14 patients had metastatic ovarian cancer. These patients had 3 or more prior chemotherapy regimens, they were vaccinated with a recombinant poxviral vaccine expressing tumor associated antigens, MUC-1 and CEA in addition to TRICOM, a set of T cell stimulatory molecules including B7.1, ICAM-1, and LFA-3. The median time to progression for those patients was 2 months (27). Viral vectors have been employed in combination to enhance immune responses through a heterologous prime boost approach (19). Vaccination targeting non-protein antigens, such as carbohydrates, has been investigated using anti-idiotypic vaccines. This methodology has been employed in ovarian cancer using anti-Ig maB ACA-125 or abagovomab. A phase I/II trial shows improved survival in patients who demonstrated antibody responses to vaccination (30). In a phase III randomized trial of patients with FIGO stage III or IV ovarian cancer in complete remission after primary surgery and platinum/taxane based chemotherapy in a placebo controlled multicenter study with RFS as the primary endpoint and OS and immunologic response as secondary endpoints. There was no improvement in either RFS or OS (35). These results and those of another multicenter phase III trial (32) suggest that CA125 is not the optimal vaccine target. Dendritic cells are antigen-presenting cells capable of initiating immune responses when they are pulsed with antigens. When these cells are stimulated with bacterial products, cytokines or CD40, maturation and migration to secondary lymphoid organs could occur. In a phase I/II study, patients with metastatic breast and ovarian cancer expressing HLA-A2 and HER2/neu or MUC1 enrolled. Dendritic cells were generated from PBMC, pulsed with peptides and injected subcutaneously on days 1, 14 and 28. Peptide specific T cell responses, were detected (33). Induced T cells are able to lyse HLA-A2 tumor cells expressing the target antigens. This approach has also been shown to expand autologous tumor reactive T cell in vitro (34,35). Use of whole tumor derivatives such as lysates to manufacture a vaccine possesses the advantage of targeting both defined antigens and undefined antigens (36). This approach, is limited as sufficient amount of tumor from a patient, needed to be harvested which may not be feasible for specific tumors or for patients in remission. Strategies that have generated immunogenicity through measurable antibody responses to glycoproteins using vaccination have not correlated with clinical responses in phase III trials (31,32). Ovarian cancer cells have been shown to express programmed death ligand 1, a ligand for the immunosuppressive T-cell receptor PD-1, which blocks T-cell responses. The expression of PD-L1 an immunoregulatory molecule, on the surface of ovarian cancer cells has been reported to be associated with poor prognosis (41). The interaction of PD-1, expressed on adaptive immune effector cells such as CD4 and CD8 T cells, with PD-L1 on ovarian cancer associated dendritic cells has been reported. In an animal model of ovarian cancer, infiltrating DCs expressed increasing levels of PD-1 and PD-L1 over time. These dual positive DCs respond poorly to signal-ing and are associated with the suppression of T cell activity and infiltration of tumors. Blockage of PD-1 reduced tumor burden and increased antigen specific T cell responses (42). This blockade of the PD-1/PD-L1 pathway is emerging as a therapeutic strategy that has shown promise in a number of solid tumors including ovarian cancer (13,43). The ovarian cancer tumor microenvironment has been shown to be immunosuppressive, and regulatory T cells have been studied. Increased frequency of CD4+CD25+FoxP3+ regulatory T-cells have been shown to predicts poor patient survival in ovarian cancer. Antibody blockage of CTLA-4 with ipilimumab has already been reported to show clinical responses in advanced ovarian cancer patients previously treated with multiple chemotherapies (11). In addition, blockage of both CTLA-4 and PD-1 can expand tumor infiltrating T cells and reduce the presence of regulatory T cells (45). It is worth noting, that combining vaccines with CTLA-4 blockage, blockage of the PD-1/PD-L1 pathway, or both could provide a platform for vaccine-induced effector and memory cells. One should note, that chemotherapy should be investigated in conjunction with therapeutic vaccination. It has been suggested that chemotherapeutic agents suppress the immune system, however reasonable evidence has emerged supporting immunostimulatory effects of these agents (47–50). In addition, chemotherapy may also recruit innate immune responses which leads to the elimination of tumor cells. Human cytotoxic T cells exposed to carboplatin or cisplatin in vitro at concentrations comparable to in vivo therapeutic concentrations did not show any decrease in CTL mediated killing (51). Exposure to platinum-based chemotherapy has also been shown to reduce the expression of T cell inhibitory molecule, programmed death receptor–ligand 2 (PD-L2) both on tumor cells and T cells increasing their immunostimulatory potential (52). Paclitaxel has been reported to increase the ability of ovarian cancer cells to activate T cells via molecule complexes of polyosome/ribosome-bound HER-2 polypeptides (53). The use of vaccination in conjunction with primary treatment could improve oncological outcome in patients with ovarian cancer. Two doses could be given prior surgery and the initiation of primary chemotherapy, as chemotherapy could conceivably have an immunostimulatory effect. Metronomic cyclophosphamide has been shown to deplete regulatory T cells, induce type I interferon, and synergize with vaccination (54). Dendritic cell vaccination with and without cyclophosphamide studied in a phase I/II trial of advanced ovarian cancer patients in remission. The authors observed, no reduction in regulatory
T cells with cyclophosphamide and no change in total lymphocytes, but those patients showed notable immunosuppression (58). To conclude, the efficacy of a therapeutic ovarian cancer vaccine will be based on factors that govern the anti tumor immune response: the quality of antigen (s), the vaccine platform, and the selection of patient population. The usage of adjuvant therapy presents may modify vaccines to direct the resulting phenotype of the immune response toward the ones favoring the prevention of cancer progression and remission.

REFERENCES


