Frontiers of Ovarian Cancer Therapy

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Since the majority of patients with ovarian cancer present with advanced stages of disease, more effective systemic approaches are needed to add to the benefits of surgical staging and debulking. New combinations of taxoids with cisplatin have prolonged survival, and other chemotherapeutic agents are being evaluated. Immunotherapy, including intraperitoneal approaches with monoclonal antibodies, cellular therapies and vaccines, hormone therapy with well-known drugs such as tamoxifen, and gene therapy give promise for the future.

Introduction

Ovarian cancer is the leading cause of death among gynecologic malignancies in the United States, surpassing the combined mortality from cervical and endometrial cancer. Approximately one in 70 women will develop ovarian cancer. In American women, it is the sixth most common cancer and the fourth most common cause of death.[1] An estimated 26,600 cases of ovarian cancer and approximately 14,500 deaths occurred in 1995.[2]

While its cause is unknown, ovarian cancer is associated with consumption of animal fat and is more common in patients with a history of breast cancer.[3] Only approximately 5% of cases are hereditary. Childbearing and oral contraceptive use reduce the risk of developing ovarian cancer by 30% to 60%, but use of replacement estrogen has no effect on the incidence.[4] Primary therapy of ovarian cancer involves adequate surgical staging and cytoreductive surgery.

Approximately 85% of patients need some form of adjuvant treatment. Platinum-based therapy has been the standard approach, with response rates of 70% to 80% and pathologic complete responses of 20% to 25%.[5] However, such therapy has minimal impact on long-term survival.[6] As a salvage therapy in patients with alkylating agent-refractory disease, platinum-based therapy induces response rates in excess of 30%.[7] The response rates for other drugs in the platinum-refractory disease are less than 20%.[6-8]

New strategies need to be generated in the treatment of ovarian cancer. The development of novel therapies has become increasingly multidisciplinary and translational in nature (Table 1). The natural agents - camptothecins and taxoids, hormonal therapy, immunotherapy including cell-mediated therapy, vaccines or monoclonal antibodies, and gene therapy - are increasingly investigated for the treatment of ovarian cancer.

Chemotherapy

Paclitaxel and Docetaxel

The taxoids, paclitaxel and docetaxel, represent a novel class of antineoplastic drugs. They share a similar mechanism of action, ie, the promotion of microtubule assembly and the inhibition of microtubule disassembly.[9] Although the molecular structures are similar, the toxicities are different. Docetaxel causes a cumulative edema but less neuropathy.[10] Both compounds have a significant clinical activity in platinum-resistant ovarian cancers (Tables 2 and 3).[11-14]

<table>
<thead>
<tr>
<th>Institution</th>
<th>Number of Patients</th>
<th>Dose (mg/m²)</th>
<th>Overall Response (%)</th>
<th>CR % (Number)</th>
<th>Median Survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Agent</td>
<td></td>
<td></td>
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<tr>
<td>James P. Hines Oncology Center</td>
<td>40</td>
<td>135 (110-FIT)</td>
<td>50</td>
<td>2.5 (1)</td>
<td>8.2</td>
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<tr>
<td>Gynecologic Oncology Group</td>
<td>41</td>
<td>170</td>
<td>57</td>
<td>12 (3)</td>
<td>15.0</td>
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<tr>
<td>Albert Einstein Cancer Center</td>
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<td>185-250</td>
<td>50</td>
<td>3 (1)</td>
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<tr>
<td>NCI-FITC</td>
<td>619</td>
<td>155</td>
<td>22</td>
<td>3</td>
<td>9.0</td>
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<tr>
<td>Eurotax</td>
<td>195</td>
<td>155</td>
<td>15</td>
<td>1 (2)</td>
<td>11.5</td>
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<tr>
<td>Canadian</td>
<td>187</td>
<td>135</td>
<td>20</td>
<td>2 (4)</td>
<td>11.5</td>
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<tr>
<td>High-Dose (with G-CSF):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>National Cancer Institute</td>
<td>44</td>
<td>210</td>
<td>40</td>
<td>14</td>
<td>11.5</td>
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<tr>
<td>M.D. Anderson Cancer Center</td>
<td>46</td>
<td>210</td>
<td>40</td>
<td>4</td>
<td>12.0</td>
</tr>
</tbody>
</table>

G-CSF = granulocyte-colony stimulating factor
CR = complete remission
The issue of dose:response with the taxoids remain unclear. Nonrandomized studies indicate a trend favoring higher or more prolonged doses. The response rates of 22% or less are seen with doses of 135 mg/m², and rates greater than 45% are seen with doses of 250 mg/m² or greater. The impact of taxoids on quality of life and survival has yet to be demonstrated. In our studies, the median survivals of patients treated with docetaxel 100 mg/m² over one hour or with paclitaxel 135 mg/m² per day and 250 mg/m² per day were 8.4 and 12.0 months, respectively, with overlapping confidence intervals. To optimize the antineoplastic activity of paclitaxel, we combined it with platinum or other agents to treat chemotherapy-naive patients. Thus, a trial was initiated to compare the standard combination of cisplatin with cyclophosphamide to the same dose of cisplatin with paclitaxel 135 mg/m².[15] The last analysis showed that the overall response rate was 64% for the standard arm and 77% for the paclitaxel-containing arm (P=0.02). The number of negative restaging laparotomies was similar.[4] and a six-month disease-free and 13-month overall survival advantage was seen in the paclitaxel arm. [15] However, complete remissions are uncommon, and the economic impact of this approach has not been addressed.

The use of paclitaxel combinations in previously untreated, suboptimal ovarian cancer patients is promising, and confirmatory trials are underway in Europe. A better understanding of dosage schedules, taxoid resistance, and integration of the taxoids into transplant settings are research priorities.

**Topoisomerase I Inhibitors**

Topoisomerase I is an enzyme necessary for the elongation phase of DNA replication and RNA transcription. It mediates the relaxation of super-coiled DNA by binding to specific regions of DNA, inducing single-strand breaks, and then rescaling the DNA breaks after uncoiling. The main topoisomerase I is an analog of camptothecin. Camptothecins bind to the topoisomerase I-DNA complex and prevent rescaling of the DNA single-strand breaks.

**Topotecan**

Topotecan, a semisynthetic, water-soluble camptothecin derivative,[16-18] has shown activity in preclinical and phase I studies. In a phase II study,[19] 30 women with refractory ovarian cancer were treated with topotecan 1.5 mg/m² daily for five days every three weeks. A 14% partial response rate was observed in patients who had prior platinum therapy. The dose-limiting toxicity was diarrhea or myelosuppression, depending on the dose schedule.[20-23] Puzzling cholinergic symptoms were observed with irinotecan.[24]

**Irinotecan**

Irinotecan (CPT-11) is a water-soluble analog of camptothecin whose metabolite, SN-38, has increased antitumor activity. An 18% to 28% objective response rate was seen with this compound in recurrent or refractory ovarian cancers. A 23% response rate was observed in patients who had prior platinum therapy. The dose-limiting toxicity was diarrhea or myelosuppression, depending on the dose schedule.[20-23] Puzzling cholinergic symptoms were observed with irinotecan.[24]

**9-Nitro-Camptothecin**

The camptothecin 9-nitro-camptothecin is a water-insoluble derivation of camptothecin that is administered orally on a continuous schedule. Preliminary data showed encouraging results in refractory ovarian cancer.[25]

**Gemcitabine**

Gemcitabine (2′,2′-difluorodeoxycytidine), a pyrimidine analogue, was developed as a new deoxycytidine analogue.[26] Gemcitabine inhibits DNA synthesis. It was originally synthesized as an antiviral agent; however, the agent was found to have excellent in vivo activity against a variety of animal tumors. Gemcitabine was given intravenously at a dose of 800 mg/m² once a week for three consecutive weeks, followed by one week of rest in platinum-refractory ovarian cancer.[27] In this phase II study, eight (19%) of the 42 patients had a partial response, with a median response duration of 8.1 months. Leukocytopenia and thrombocytopenia were the main toxic effects. Gemcitabine is a well-tolerated drug with activity in platinum-resistant ovarian cancer patients.

**Suramin**

Suramin, a polysulfonated naphthylurea, is a nonspecific growth factor antagonist used in the treatment of patients with metastatic cancer. It exerts an antiproliferative effect on a variety of human cancer cell lines grown in vitro,[28,29] possibly by inhibition of signal transduction pathways.[30,31] The effects of suramin combined with cisplatin were tested in a nude mouse model of human ovarian cancer.[32] When cisplatin was followed by 5 or 10 mg/m² suramin, the tumor formation rate was less than 20%. If suramin was followed by cisplatin, no tumor formation was observed during the experimental period. A phase II clinical trial[33] in 10 patients with platinum-resistant refractory ovarian cancer demonstrated no objective responses, but three of nine evaluable patients experienced disease stabilization and subjective clinical improvement for periods ranging from two to five months.

**Immunotherapy**

Increasing research has been devoted to intraperitoneal approaches. However, durable responses impacting on survival are lacking.

**Monoclonal Antibodies**

Monoclonal antibodies linked to radioisotopes have been used for palliation of ascites. Characteristics of yttrium 90 (⁹⁰Y) make it suitable for use with monoclonal antibodies.[34,35] Current phase II trials are aimed at using the agent intraperitoneally for the relief of symptomatic ascites. The radiolabeled antibody conjugate, ⁹⁰Y-CYT-103, has been administered by the intraperitoneal route to patients with ovarian cancer.[36] Tumor-binding and favorable dosimetry were demonstrated after laparotomy.[37] Meaningful radiation doses are now possible with 40 mCi of ⁹⁰Y. Relief of ascites was reported in two studies using AB263-13I or NMFG-⁹⁰Y. A second-generation B7.2 MoAb, known as CC49, has greater avidity for the target antigen, TAG-72. Further studies are ongoing for the treatment of minimal residual disease and/or palliation of ascites.[39]

**Adoptive Immunotherapy**

Potentiation of an autologous tumor-specific immune response is the central goal of biologic therapy of cancer. Potential mechanisms involved in this antitumor effect include the activation of lymphokine-activated killer (LAK) cells, the generation of cytotoxic T-lymphocytes against the tumor, and the secondary induction of other cytokines such as tumor necrosis factor-alpha (TNF-alpha) or interferon gamma. Major clinical responses, including durable complete remissions, were observed in...
cancer patients treated with ex vivo activated LAK cells and high doses of recombinant interleukin-2. Complete and partial response rates in initial clinical trials approximated 20% in ovarian cancer.[40,41] Two recent trials report results of adoptive immunotherapy. Tumor-infiltrating lymphocytes were expanded from malignant lesions and reinfused intraperitoneally with low-dose interleukin-2. In this pilot study, four of eight patients exhibited clinical indicators of biologic activity including reduction of ascites in two patients, reduction of tumor and CA-125 value in one patient, and surgical confirmation of stable disease with stable CA-125 values in one patient.[42] At the present, intraperitoneal priming with recombinant interferon gamma followed by recombinant interleukin-2 for ex vivo expansion of activated tumor-infiltrating lymphocytes in intraperitoneal adoptive immunotherapy is being investigated. Clinical response was noted on intraperitoneal administration of antibody-labeled lymphocytes.[43]

**Vaccine Therapy**

By using synthetic carbohydrate and peptide-based antigens, large quantities of pure vaccine material may be produced without contamination of cellular antigens. An example is the sialyl-Tn (STn) antigen that is an epitope of TAG-72 recognized by the MoAb B72.3. STn antigen is an epitope of mucin that in high levels is known to be associated with poor prognosis in patients with cancer.[44,45] It also is a target for antibody-dependent cellular cytotoxicity.[46]

The STn antigen is conjugated to the carrier keyhole limpet hemocyanin (KLH) and administered in the adjuvant Detox-B SE. As the soluble antigens can induce suppressor T-cell activity, inhibiting an effector response to the cancer-associated antigen, so active-specific immunotherapy is preceded by administration of a low-dose cyclophosphamide to reduce or eliminate the putative suppressor T cells.[47-50] In breast cancer patients, hapten-specific humoral responses have developed, and antibodies are produced that are cytotoxic in vitro to tumor cells in the presence of complement.[51] There is an inverse relationship between the antibody response and delayed-type hypersensitivity response as a function of antigen dose.[52] and a strong and stable cell-mediated Th1-type response may be induced by low doses of antigen.[53] A trial is underway in rodents to evaluate immune response to the vaccine with two different doses by measuring complement and antibody-dependent cellular cytotoxicity, immunoglobulin G and M levels, lymphocyte phenotype, and various cytokine levels.

Another approach involves autologous tumor-cell vaccination followed by lymphokine-activated tumor-infiltrating lymphocytes (LAK-TILs). The generation of cytotoxic effector cells from TILs was done by adding recombinant interleukin-2. TILs isolated in this way have an increased percentage of CD8 and CD16 positive cells compared to peripheral lymphocytes, with a marked increase in cytotoxic activity against tumor cells. The remission rate achieved was 41% for five months. It is too early to determine the effect of this therapy on survival.[54]

Chemotherapy may yield better results when the standard treatment is combined with active-specific immunotherapy. Twenty-four patients with stage III ovarian cancer underwent a primary tumor reductive surgery followed by three courses of active-specific immunotherapy and six courses of platinum-based polychemotherapy. Fifteen achieved a complete remission, eight had a partial remission, and one had progressive disease. The median disease-free survival in patients with complete remission was up to 30 months. However, these data need to be confirmed.[55]

**Hormone Therapy**

Treatment options are limited for patients who have persistent or recurrent ovarian cancer following platinum- and paclitaxel-based chemotherapy.[56] Treatment with further chemotherapy yields not only low and transient response rates but also marked toxicity, higher expenses, and questionable effects on quality of life. Hormonal therapy, however, is an attractive nontoxic option.

Reports on tamoxifen used for persistent or recurrent epithelial ovarian cancer indicate response rates that vary from 0% to 27%. [57-65] The combined result of all studies is an 11.1% complete response rate, including 4.7% complete responses and 33.3% stabilization of disease. It is difficult to predict which patients will benefit from tamoxifen treatment as there is no apparent difference in histologic subtypes, grade of tumor, or hormone receptor values between responders and nonresponders.[61,63] Tamoxifen has minimal side effects and may induce complete responses in persistent and recurrent ovarian cancer. It is best initiated when there is a progressive rise in CA-125 titers, before gross evidence of recurrent disease. Quality of life usually is excellent and can be maintained for an average duration of nearly 12 months. Tamoxifen also may have a role as maintenance therapy in patients having completed chemotherapy.

One possible mechanism of action of tamoxifen is that it interacts with type II estrogen-binding sites and its binding affinity correlates well with its growth inhibitory effects.[66,67] Synergistic in vitro activity was noted when tamoxifen was combined with either cisplatin or doxorubicin.[68] The addition of tamoxifen in vitro produced a potentiation of cisplatin activity up to 50-fold.[69] However, a prospective, randomized trial[70] reported no benefit of tamoxifen (20 mg/m² per day) in overall and progression-free survival. It is now conceivable that tamoxifen should be administered at doses higher than those conventionally used in breast cancer in order to achieve the synergistic effect with cisplatin.[69] Prospective clinical trials are needed to evaluate this possibility.

Gonadotrophin-releasing hormone (GnRH) analogs have gained much interest in the past few years as a nontoxic, second-line treatment of ovarian cancer. Low-affinity[71,72] and high-affinity[73] GnRH binding–sites have been identified and characterized in epithelial ovarian cancer. GnRH analogs have a direct suppressor effect on ovarian tumors using a cell regulatory pathway rather than a toxic mechanism. GnRH agonists, with different regimens, have been used in the treatment of advanced, recurrent, or persistent ovarian carcinoma. The combined results have shown a 12% response rate with 30% stable disease.[74] Most studies involved poor prognosis patients who were heavily treated with chemotherapy. In animal studies, the response to GnRH agonists is characterized by latency and transience,[75] which has led to the search for more effective GnRH analogs.

Luteinizing hormone-releasing hormone (LHRH) cetrorelix is a pure antagonist that has caused significant reduction in tumor volume, tumor burden, and prolongation of the tumor's doubling time in animal models. It reduced the concentration of receptors for epidermal growth factor and insulin-like growth factor 1 in tumors. These may be related to tumor growth inhibition.[76] Pure LHRH antagonists such as SB-75 might prove to be superior to LHRH agonists in the treatment of advanced ovarian carcinoma. In view of its powerful inhibitory effect on OV-1063 tumors and lack of side effects, SB-75 could be considered for treatment of advanced epithelial carcinomas.[77]

**Gene Therapy**

Although gene-therapy approaches to ovarian cancer have been disappointing so far, one tactic of gene therapy involves chemosensitization by transduction of so-called suicide genes. This approach entails the introduction of a herpes simplex virus-thymidine kinase (HSV-TK) transcription unit into cells. Viral thymidine kinase molecules are released into dividing tumor cells. The cells then become sensitive to systemically administered ganciclovir, an agent that is innocuous in nontransduced cells. Freeman et al.[78] demonstrated that HSV-TK-positive cells exposed to ganciclovir were lethal to HSV-negative cells as the result of a “bystander effect.” HSV-TK-negative cells were killed in vitro when the population of cultured cells contained only 10% HSV-TK-positive cells. The mechanism of this “bystander effect” is not clear. The toxic effect of HSV-TK-positive cells on HSV-TK-negative cells was reproduced in an in vivo model. The “bystander effect” also was demonstrated in intraperitoneal tumor studies. The first human gene therapy protocol was developed using HSV-TK-modified tumor cells to treat ovarian cancer patients.[79]

Genetic modification for chemoprotection is under active study. In rodents, it has been demonstrated that the human multidrug-resistant (MDR)-1 cDNA may be
transduced by a safety-modified retroviral vector. The rodents are then relatively resistant to the myelosuppressive effects of paclitaxel.[80] Such a transduction can be accomplished in human CD34+ cells ex vivo with a 20% efficiency. Again, there is a resulting resistance to the cytotoxicity of paclitaxel.[81] Studies with platinum compounds and paclitaxel tend to support a dose response, but toxicity is the limiting factor. Even with cytokine support, higher doses of paclitaxel result in significant dosage reductions and hematologic toxicities. A trial of MDR genetic transduction into the CD34+ cells of patients has been conducted to determine whether this allows greater paclitaxel dose intensity in refractory or recurrent ovarian cancer. Ideally, the significant increase in p-glycoprotein product in CD34+ cells will confer protection against MDR-mediated drugs. Ten patients have undergone transduction with an efficiency of 1% to 3%, and paclitaxel therapy has been started. If the technique is successful, it may provide a new strategy for improving dose intensity.

Conclusions

The development of novel therapies in ovarian cancer appears promising. The rediscovery of taxoids and camptothecins has yielded potentially beneficial compounds. A more precise knowledge of the mechanisms of action of steroids has sparked a renewed interest in hormonal therapies. Increased understanding of the mechanism of drug action and its resistance should improve their therapeutic efficacy. The fields of immunology and molecular biology are emerging, with trials using monoclonal antibodies, cellular therapies, and vaccines. Exploration of the genome has already allowed human genetic modification therapies.

References


Clerici M, Shearer GM. A Th1-Th2 switch is a critical step in the etiology of HIV infection. Immunology Today. 1993;14:107-111.


