REVIEW ARTICLE

CANCER OVARY, PRESENT AND FUTURE OF MANAGEMENT

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Ovarian cancer is very important malignancy of woman as far as its incidence and mortality is concerned. Although majority presents at late stage but still there is a reasonable response to currently available chemotherapy drugs and their use in multimodality setting. Besides good response to chemotherapy drugs, majority have recurrence. So there is a need for new drugs, new trends and their combinations. All these issues will be discussed in this review article.

INTRODUCTION

In the western world cancer ovary is the fifth leading cause of cancer death among the women[1]. The incidence is higher in older age and the median age at diagnosis is 61 years[2]. In one of the study done in Pakistan ca ovary was the 4th prevalent cancer in the hospitals of Lahore[3].

The most important risk factor for ovarian cancer is having a family history of a first-degree relative, i.e., genetic background[4]. Majority present with advanced disease, but most of them responds to initial therapy however the relapse rate and mortality is high[5].

PRESENT TREATMENT

First line therapy

Cisplatin and paclitaxel combination proved better over the previously established combination of cyclophosphamide and cisplatin as the initial therapy for advanced ovarian cancer almost a decade ago[6]. Initials reports of higher toxicity with this combination has been lowered with the use of 24-hour infusion of paclitaxel in this combination instead of the initially used 3 hour infusion[7].

The combination of paclitaxel and carboplatin is more attractive alternative due to lower incidence of non-haematologic side effects and easy outpatient management[8]. It also had a significantly better quality of life[8].

Although the two paclitaxel-based combinations with either carboplatin or cisplatin are equivalent in treatment results, the paclitaxel/ carboplatin combination is more attractive because of the easy administration and lower side effects. Currently, this combination serves as a control arm in most of the prospective randomized phase 3 trials.

Docetaxel is another alternative to paclitaxel but there were no difference in response and progression-free survival[9]. However, docetaxel/ carboplatin combination may be considered for patients where an unacceptable severe neurotoxicity is expected, such as in patients with diabetes mellitus[9].

Different studies comparing the effects of monotherapy versus combination has shown that single-agent carboplatin was better due to toxicity profile so platinum monotherapy can be a reasonable alternative as first line therapy but this need more clarification[10].

Intraperitoneal (IP) chemotherapy with cisplatin have provided a better therapeutic index in combination with other regimens[11]. Whether this should be a part of the regimen, more studies are required to be done[12].

Because of the vast majority of relapses after initial therapy, the institution of consolidation or maintenance therapy seems to be a promising way to improve survival rates but until now the results are not encouraging[13].

Addition of a non-cross resistant agent to the platinum/paclitaxel combination in the first-line therapy like anthracycline, topotecan or gemcitabine have shown varying results[14].

The combination of paclitaxel and carboplatin plus pegylated liposomal doxorubicin, topotecan, or gemcitabine is being evaluated by the GOG 182 study. This study is expected to run through 2004[15,16]. Until the results of these studies are available, there are insufficient data to support the addition of a third drug to the platinum/paclitaxel combination as first-line therapy for ovarian cancer outside of a clinical trial.

Second-line therapy

Although first-line therapy in advanced ovarian cancer have high response rates but up to 80% relapses[17]. Currently, there is no widely accepted standard therapy for relapsed disease; however, several agents have been studied, including paclitaxel, oral etoposide, topotecan, gemcitabine, pegylated liposomal doxorubicin, tamoxifen, and platinum-based regimens. All these agents in different studies have shown varying response rate[18-25].

The choice of second-line therapy largely depends upon the interval from the completion of platinum-based first-line therapy to relapse. Patients who progress on first-line platinum therapy are said to have platinum-refractory disease; those who relapse within 6 months are considered to have platinum-resistant disease; and those with a relapse-free interval of at least 6 months are said to have potentially platinum-sensitive disease. Thus, in general, patients who have had a disease-free interval of at least 6 months should be considered candidates to receive another platinum-based regimen. Indeed, a number of studies have demonstrated impressive response rates with a second platinum-based regimen in this patient population.

A second-line regimen of 135 mg/m^2 paclitaxel via 24-hour IV infusion followed by 50 mg/m^2 IV cisplatin demonstrated an overall response rate of more than 50% in both platinum-resistant and platinum-sensitive patients; median survival was more than 20 months for responders in both groups[22]. A 3-hour infusion of paclitaxel 175 mg/m^2 followed by a 30-minute carboplatin infusion (AUC 5) demonstrated a 70% overall response rate and a 14-month median survival in platinum-sensitive patients[23].

As with first-line therapy, the idea of monotherapy offers several potential advantages. It is not necessary to compromise the dose due to the combination, and a single agent is generally less toxic. A second-line regimen of paclitaxel 135 mg/m^2 via 24-hour infusion every 3 weeks demonstrated an objective response rate of 22% and a median survival of 8.8 months[21]. As this agent moved into front-line therapy, there was a need for newer active agents in relapsed disease.

Two newer agents have been extensively studied, including in randomized phase 3 trials. In a phase 3 trial, 226 patients with ovarian cancer who had progressed after first platinum-based regimen received 1.5 mg/m^2 topotecan via 30-minute infusion daily for 5 days or 175 mg/m^2 paclitaxel infused over 3 hours every 21 days[25]. Response rates between the groups were similar: platinum-resistant patients demonstrated a response rate of 13.3% with topotecan vs a rate of 6.7% with paclitaxel, while platinum-sensitive patients demonstrated a response rate of 28.8% with topotecan vs a rate of 20% with paclitaxel. Although a significant improvement with topotecan vs paclitaxel was initially noted in the median time to progression, longer-term follow-up demonstrated no significant difference between the groups[26].

Given the significant survival advantage with pegylated liposomal doxorubicin over topotecan in patients with platinum-sensitive disease and its equivalence to topotecan in patients with platinum-resistant disease, pegylated liposomal doxorubicin emerges as an important monotherapy option for patients with recurrent ovarian cancer.

To date, there are no randomized trials that have demonstrated a benefit of combination therapy over monotherapy in the second-line setting. The question of monotherapy vs combination therapy in recurrent ovarian cancer is also being explored in a number of other trials. For example, trials evaluating the combinations of pegylated liposomal doxorubicin plus carboplatin, gemcitabine plus carboplatin, and pegylated liposomal doxorubicin plus gemcitabine are currently under way by the Southwest Oncology Group. Data from all of these trials may help to identify a combination that can improve upon current single-agent treatments.

When selecting a therapy, it is important to remember that the goal of second-line therapy is palliation; therefore, improving or maintaining the patient's quality of life must be a priority.

Because each of the active agents in recurrent ovarian cancer has a unique mechanism of action, the toxicity profiles are often nonoverlapping. It is therefore easier to identify more favourable or less favourable toxicities based on patient preference and/or available supportive therapies. For example, in trials with both pegylated liposomal doxorubicin and topotecan, paclitaxel was associated with a greater incidence of alopecia, which can confer negative psychological effects on patients and which cannot be reversed until after therapy has been discontinued[25,27]. Similarly, topotecan was associated with a greater incidence of myelosuppression when compared with pegylated liposomal doxorubicin, resulting in greater use of haematopoietic growth factors and dosing modifications[20].

Patient compliance and preference has also emerged as an important consideration in selecting a therapeutic option. Because the 3 proven active monotherapy agents are all administered via IV infusion, the duration of infusion and the frequency of administration can serve as points of differentiation. For example, although the duration of topotecan infusion is only 30 minutes, the 5-times-weekly regimen might prove difficult for some patients. Overall, when the primary goal of therapy is palliation, patient preference and compliance is of paramount importance.

Surgical Intervention in Advanced Cancer

The value of debulking surgery in the management of advanced ovarian cancer has been demonstrated by a randomized EORTC study, which showed a benefit in both progression-free and overall survival with debulking surgery[28]. Patients with residual disease after primary surgery of at least 1 Cm were treated with 3 cycles of cisplatin and cyclophosphamide. Those who had a complete or partial response or stable disease were then randomized to debulking surgery or to no surgery, followed by 3 more cycles of cisplatin and cyclophosphamide. The median survival was 6 months longer in the group with debulking surgery vs the other that did not have surgery (26 months vs 20 months).

FUTURE THERAPIES

Despite the progress made in chemotherapy regimens, the majority will relapse and eventually die of their disease. Although a number of newer chemotherapeutic agents are being developed, much of the focus of research efforts has shifted toward novel agents, including immunologic agents (such as vaccines) and targeted agents toward specific molecular pathways.

Immunotherapy

One area of interest is in the development of monoclonal antibodies directed against CA-125. Oregovomab, a monoclonal antibody with high affinity to CA-125, has been studied in patients with ovarian cancer[29]. Patients who developed immunologic responses had a 2-fold longer median time to relapse compared with those who did not have immune responses. Another approach is to vaccinate patients with an anti-idiotype CA-125 monoclonal antibody, which has shown response in 60% of ovarian cancer patients whose outcome is significantly better than that of nonresponder patients[30].

IM862 is a synthetic version of a naturally occurring peptide (L-glutamyl-L-tryptophan) that stimulates the immune system and inhibits angiogenesis. The drug has a very small molecular weight, making it absorbable

through mucous membranes and allowing for intranasal administration. Doses from 5 mg every other day to 120 mg per day studied in a phase ½ trial were well tolerated[31].

Molecularly Targeted Therapy

The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib and erlotinib are currently being studied in ovarian cancer. These agents are attractive because they are administered orally and are associated with minimal adverse effects. Preclinical data suggest that gefitinib may act synergistically with chemotherapy in ovarian tumours that have high expression of the epidermal growth factor receptor[32,33]. The NCIC is currently conducting a phase 2 study of erlotinib in combination with carboplatin in relapsed ovarian cancer.

Vascular endothelial growth factor (VEGF) overexpression in ovarian cancer cells is thought to be an important factor in tumour angiogenesis and biologic aggressiveness. A number of agents are being developed to target VEGF in the treatment of various solid tumours. Bevacizumab is a recombinant monoclonal antibody to VEGF that has been studied in a number of solid tumours including renal cell, colorectal, and lung cancer. The GOG is currently conducting a phase 2 trial of bevacizumab in the treatment of persistent or recurrent ovarian cancer.

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