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Perspectives and Commentaries

Present Optimal Therapy in Ovarian Cancer

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(A COMMENT ON: Aabo K, Hald I, Hørbor S *et al.* A randomized study of single agent vs combination chemotherapy in FIGO stages II_B, III and IV ovarian adenocarcinoma. *Eur J Cancer Clin Oncol* 1985, **21**, 475–481).

INTRODUCTION

ANALYSIS of medical progress over the past few years in epithelial ovarian cancer reveals mixed results. The disease remains the leading killer among gynecologic cancers and is the fourth most frequent cause of cancer deaths in women. Overall 5-yr survival remains less than 40%, reflecting the fact that of all malignancies, ovarian tumors present most frequently in advanced stages [1]. However, pessimism should be tempered by the almost 80% complete and partial response rate achieved with our current therapeutic armamentarium [2, 3]. Several prospective carefully controlled trials have proven that these responses do indeed translate into increased relapse-free and median survival, especially when aggressive approaches are optimally applied [2, 4].

In this neoplasm a multidisciplinary approach using surgery, radiotherapy and chemotherapy has improved treatment results. Future progress will continue to depend on the creative integration of these different disciplines. To better appreciate their respective roles, it is helpful to review separately their contributions to date and promising ongoing research.

CHEMOTHERAPY

Single agents

Alkylators were the first group of drugs widely used in ovarian cancer, with response rates of 25–50% [2, 5]. Importantly, alkylating agents alone can be curative in 5–10% of patients with advanced disease [6]. Choice among alkylators is based mostly on avoidance of drug-specific toxicities rather than on response criteria as the different agents available, melphalan, chlorambucil, cyclophosphamide and dihydroxybusulfan, have shown similar response rates [5, 7]. Initial trials using high-dose intravenous cyclophosphamide or intraperitoneal melphalan, designed to overcome tumor resistance by increasing the drug levels reaching the tumor, have not demonstrated improved response rates [8, 9]. This probably indicates a shallow dose–response curve for alkylators in this disease. Yet novel approaches such as the enzymatic degradation of circulating amino acids such as glutamine, which competitively inhibit melphalan uptake into tumor cells, may provide other mechanisms for overcoming tumor resistance [10].

Doxorubicin yields response rates similar to alkylating agents in untreated patients [11]. Unfortunately, the mean duration of response is 3 months due to rapid development of resistance. Recent studies have confirmed the mechanism of this resistance by showing that tumor cells can develop new chemical pathways permitting increased clearance of doxorubicin from the malignant cells [12]. Based on these findings, efforts to reverse this active pump in tumor cells have been undertaken with verapamil, a calcium channel blocker, that seemingly interferes with this efflux mechanism [13].

Hexamethylmelamine also has proven effectiveness in this disease and offers the advantages of minimal myelotoxicity coupled with a significant 20% response rate in previously treated patients [14]. This apparent cross resistance has encouraged its use in several combination chemotherapy regimens [15].

The most active drug in ovarian cancer is cispla-

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tin because of its ability to induce complete remissions even in pretreated patients [16]. A steep dose–response curve has been defined for this agent, rendering appeal to techniques such as intraperitoneal chemotherapy or high-dose systemic therapy [17, 18]. Because of its importance, yet burdensome side-effects, analogs of cisplatin with reduced toxicity have been developed. Two such compounds, carboplatin (JM8) and CHIP (JM9), have shown comparative response rates with reduced nephro-, neuro-, oto- and gastrointestinal toxicity but greater myelotoxicity in phase II trials [19, 20]. Carboplatin is undergoing phase III comparison with cisplatin in a current randomized EORTC trial.

Other drugs such as 5-fluorouracil, methotrexate and more recently hormonal agents have shown limited activity in ovarian cancer. A thorough review of all new compounds undergoing testing is not possible here but has recently been presented [21].

Combination therapy

Similar to the evolution seen in breast, testicular and small cell lung cancers, multiagent treatment regimens using various combinations of the abovementioned drugs are now used extensively in ovarian cancer. Although response rates are clearly higher using this approach, a prolongation of median survival compared to single-agent therapy has been harder to prove [see Aabo *et al.* in an earlier issue of this journal]. Like other group studies that have not clearly shown survival benefits, this Denmark group result still hints at advantages for combination therapy due to the higher complete response rates obtained in their combination arm (24%) vs single-agent treatment (13%).

Newer combination regimens containing cisplatin have further increased the ability to obtain a pathologic complete response (PCR). Such combination treatments have now demonstrated improved duration of remission and survival compared to single-agent therapy [2, 4]. Since response rates in relapsed patients with second-line regimens are uniformly less than 50%, only patients obtaining PCR can have high hopes of long-term survival. This justifies an aggressive initial approach with combination chemotherapy in all patients with advanced ovarian cancer.

Examination of almost all recent studies reveals that a high rate of PCR occurs predominantly in patients with minimal residual disease post-staging laparotomy [22]. For this minimal residual disease group, which represents less than 30% of all patients with advanced ovarian cancer, long-term survival, even cure, seems probable for approximately 40–70% of those patients obtaining PCR with current combination chemotherapy [22]. In patients with bulky disease post-laparotomy (nodules > 2 cm), PCR drops sharply to 10–20%. As this group represents the majority of ovarian cancer patients, it is understandable that overall 5-yr survival rates have changed minimally in this disease in the past few years.

Choosing the optimal regimen among the different combinations tested so far is difficult. However, the study by the Netherlands Ovarian Cancer Group comparing HEXA-CAF (hexamethylmelamine, cyclophosphamide, methotrexate, 5-FU) to CHAP-5 (cyclophosphamide, hexamethylmelamine, adriamycin, cisplatin) convincingly supports the use of a cisplatin-containing combination [23]. Hopefully continued prospective randomized trials will clarify the optimal regimen to use in the future.

RADIATION THERAPY

Comparable to chemotherapy, response to radiation is most beneficial when disease volume is minimal. Most trials have therefore explored the value of radiotherapy in early stage disease or in minimal residual disease post-laparotomy. Because occult spread of ovarian cancer occurs throughout the abdominal cavity, only radiation techniques (abdomino-pelvic [24] and intraperitoneal radiocolloid [25]) that encompass the entire zone at risk are currently used.

Prospective randomized trials with pretreatment surgical staging have not revealed an advantage in women with stage I or II completely resectable disease for abdomino-pelvic radiation or intraperitoneal radiocolloids vs single-agent chemotherapy. Furthermore, survival in these carefully staged patients is excellent, varying between 80–90% at 2 yr with surgery alone, rendering the study of possible benefits of adjuvant treatment quite difficult [22].

Lacking definitive trials, physicians faced with this infrequent presentation of early-stage ovarian cancer must use prognostic factors to guide them in deciding on post-surgical therapy. Patients with risk factors such as high grade ($\geq$2), dense tumor adherences at surgery and positive peritoneal cytology should receive adjuvant therapy in a randomized treatment protocol comparing radiation treatment to chemotherapy. In the absence of such studies, therapeutic decisions between chemotherapy and radiotherapy should be based on individual and institutional experience with these methods.

For patients with stage III minimal residual disease, both abdomino-pelvic radiation and combination chemotherapy yield 60–70% PCR rates, with approximately 2/3 of these patients alive at 5 yr. Only further randomized trials with scrutinous staging requirements will permit comparisons of efficacity vs toxicity of these two treatments. An

added important benefit of such studies will be the determination in non-responders of selective risk factors permitting new approaches in this resistant group.

COMBINED MODALITY TREATMENTS

Surgical debulking of advanced ovarian cancer has gained widespread acceptance because, as we have seen, the effects of radiation and chemotherapy in this disease are inversely proportional to tumor volume. Aggressive initial staging operations, often followed by second- and sometimes third-look laparotomies, have been utilized to assess response and remove persistent disease in the hopes of improving the results of subsequent treatment. Several studies have shown that survival is definitely superior in patients with minimal residual disease < 2 cm irrespective of post-surgical therapy [26].

This observation has prompted attempts in patients with unresectable disease at initial staging to use pre-operative chemotherapy or radiotherapy to cytoreduce these patients and thereby render debulking surgery possible. Although such an approach has been successful in 40–70% of stage III patients initially judged unresectable, it has not improved the prognosis for these patients [22]. In other words, women with bulky disease who are difficult to easily convert to minimal disease status at the time of initial presentation appear to have more resistant tumors regardless of our ultimate ability to effectively cytoreduce their disease. These patients relapse early and do not respond completely to chemotherapy as do patients with minimal disease from the outset.

To convert incomplete responders to chemotherapy into complete remission, abdomino-pelvic radiation has been administered to patients with persistent minimal residual disease after combination chemotherapy. However, improved survival has not been demonstrated with this approach [27]. Pushing this combined therapy concept even further, workers at the NCI in the United States are now studying alternating monthly radiotherapy with chemotherapy and so far have not encountered prohibitive toxicity [24].

CONCLUSION

Although advanced ovarian cancer remains lethal for the majority of its victims, controlled clinical trials have permitted clarification of important risk factors and determination of effective therapy in the minimal residual disease group. Improvement in survival for the patients with bulky disease has been slower. Yet the potential of combined modality treatment coupled with new pharmacologic methods to reverse drug resistance and enhance cellular drug levels with intraperitoneal and high-dose systemic chemotherapy should hasten future progress.

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