CME CREDIT

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The genetics, screening, and treatment of epithelial ovarian cancer: An update

ABSTRACT

Recent genetic findings are shedding light on who is at risk for epithelial ovarian cancer, by far the most common of ovarian malignancies. Current screening tests are inadequate, but a serum test of lysophosphatidic acid shows promise. Clinical trials show that cisplatin or carboplatin plus paclitaxel increases progression-free and overall survival times vs regimens that do not contain paclitaxel, and that a carboplatin-paclitaxel regimen is less toxic than cisplatin-paclitaxel and can be given on an outpatient basis. The development of newer cytotoxic drugs and alternative routes of administering chemotherapy offers hope of improved survival for women with advanced ovarian cancer.

Genetic abnormalities account for only 5%–10% of cases

SIGNIFICANT ADVANCES have been made during the past 5 years[1] in our understanding of the biology, genetics, screening, and treatment of epithelial ovarian cancer, by far the most common ovarian malignancy. New treatments offer hope for improved survival in patients with advanced disease, and preliminary work holds promise for a simple blood screening test to detect epithelial ovarian cancer sooner.[2]

PATIENT CHARACTERISTICS AND RISK FACTORS

Although less common than cervical or uterine cancer, epithelial ovarian cancer causes more deaths than the other two combined,[3] as it is usually diagnosed in its later stages, when treatments are less effective and survival is lower. The average age at diagnosis is 55 years.

Risk factors for ovarian cancer include low parity and a history of breast or colon cancer. Ovarian cancer is more common in industrialized countries, which suggests the importance of as yet unidentified environmental factors.

BRCA1, BRCA2 account for a minority of cases

Family history has long been recognized as an important risk factor for epithelial ovarian cancer.[4] For example, a woman with two first-degree female relatives with epithelial ovarian cancer has a 50% lifetime risk.

Researchers have identified genetic abnormalities strongly linked to hereditary cancers of the ovary and the breast.[5–7] An estimated 7% to 10% of women with ovarian cancer have an autosomal-dominant mutation that markedly increases the risk of ovarian cancer.[8] Two specific foci (*BRCA1* on the long arm of chromosome 17, and *BRCA2* on the long arm of chromosome 13) have been suggested as responsible for perhaps 90% of all cases of hereditary ovarian cancer. Overall, approximately 4% of women with epithelial ovarian cancer have abnormalities in *BRCA1*, and 3% have abnormalities in *BRCA2*.

A recent study[8] found that 2% of women with ovarian cancer who do not report a family history have either the *BRCA1* or the *BRCA2* mutation. In contrast, 10% of women who report having a second-degree relative with ovarian cancer have the genetic abnormality, as do 15% of women who report having a first-degree relative with ovarian cancer. Therefore, although a positive family history increases the chance of a genetic abnormality,

only a minority of women with ovarian cancer (even those with a strong family history) have a genetic mutation to account for the development of the cancer—5% to 10% overall.

Clinical implications of the genetic findings

We do not have enough data to make any precise recommendations for women with a strong family history of epithelial ovarian cancer (either by history alone, or by the documented presence of genetic abnormalities). Although some investigators recommend prophylactic oophorectomy when child-bearing is complete, even oophorectomy does not eliminate the risk of ovarian cancer, as the entire peritoneal lining is potentially at risk for the development of an ovarian cancer-like malignancy (eg, primary carcinoma of the peritoneum).

Screening for *BRCA1* and *BRCA2* abnormalities does not yet have a defined role, except in research. At a minimum, if a woman wishes to undergo such testing she should discuss the implications of the test findings with a physician knowledgeable in cancer genetics. Issues of insurance and job discrimination based on the results of genetic testing remain unresolved.

Of interest, two recent studies[9,10] suggested that while an abnormality in *BRCA1* increases the risk of ovarian cancer, patients with the disease and this specific genetic mutation survive longer than women who have the same stage and grade of tumor but not the mutation. An adequate explanation for this fascinating observation is not currently available.

SIGNS AND SYMPTOMS ARE NONSPECIFIC

In 70% of cases, epithelial ovarian cancer is diagnosed late, after it has spread throughout the abdominal cavity (stage III). This is because there are few if any early signs of ovarian cancer, and it easily and rapidly diffuses in the peritoneum once it has penetrated the surface of the ovary. Signs and symptoms that do develop are nonspecific (eg, pelvic or abdominal pressure and pain, abdominal swelling, fatigue, early satiety). As the disease advances, patients experience weight loss and greater pain, sometimes progressing to bowel or ureteral obstruction.

OVARIAN CANCER IS DIFFICULT TO DETECT EARLY

Unfortunately, no established, sensitive, and specific method has been found to diagnose ovarian cancer, making it difficult to find while it is still confined to the ovary.

Pelvic examination rarely detects cancer early

Pelvic examination rarely detects early-stage ovarian cancer, either during a routine physical or during evaluation for nonspecific abdominal or pelvic discomfort. Even cases of ovarian cancer discovered on pelvic examination often prove to be in their advanced stages on surgical assessment.

Normally, the ovaries are not palpable in postmenopausal women, owing to normal atrophy. Therefore, if a postmenopausal woman presents with nonspecific pelvic discomfort and her ovaries are palpable, further evaluation for the presence of more serious pathology should be undertaken with ultrasound or computed tomography.

The Papanicolaou smear, while extremely useful in detecting cervical cancer, is of no clinical value in detecting ovarian cancer.

After menopause, palpable ovaries are abnormal

Serum CA-125 testing: neither sensitive nor specific

Serum levels of carbohydrate antigen 125 (CA-125) are elevated in 80% to 90% of women with advanced disease, but they are within the normal range in 50% of women with surgically documented stage I disease. Therefore, although CA-125 is often used as a screening test, it lacks sensitivity.

This antigen has also been shown to be quite nonspecific, with elevated levels demonstrated in a number of malignancies (eg, breast, pancreas, colon, gastric cancer) and benign disease states (eg, pregnancy, endometriosis, pelvic inflammatory disease, cirrhosis, hepatitis).

Lysophosphatidic acid shows promise

In a preliminary report[2] from the Cleveland Clinic, investigators showed that the growth-stimulatory factor lysophosphatidic acid, present in the ascitic fluid of women with epithelial ovarian cancer, was elevated in the plas-

ma of 9 of 10 women documented to have stage I disease at the time of exploratory laparotomy.

While lysophosphatidic acid was also elevated in other malignant and benign gynecologic diseases and in a small percentage of normal subjects, the apparent sensitivity of this marker for early-stage ovarian cancer leads to hope that a simple blood test may serve as a screening strategy for ovarian cancer. However, before it can be considered a standard test in routine clinical practice, further research is required to confirm and define both its sensitivity and specificity.

Routine screening not yet recommended

Lacking evidence that screening with either CA-125 or lysophosphatidic acid reduces mortality from ovarian cancer, we must conclude that routine screening is not yet proven to be effective for any subgroup, including women with a positive family history.

FACTORS THAT INFLUENCE SURVIVAL

Standard chemotherapy includes platinum agents plus paclitaxel

Factors that significantly influence survival in ovarian cancer include:

- Stage of disease (FIGURE 1)
- Amount of residual cancer after initial cytoreductive surgery ("debulking")
- Tumor grade
- General health status
- Patient age.

Survival is strongly influenced by the stage of disease at diagnosis. Five-year survival is highest when the cancer is confined to the ovary, and lowest when it has spread beyond the abdominal cavity.

DEBULKING SURGERY RECOMMENDED

For most women with epithelial ovarian cancer, initial management includes exploratory laparotomy followed by systemic chemotherapy.[1] The surgeon removes ("debulks") as much tumor as possible at laparotomy, as extensive retrospective experience shows that patients who start chemotherapy with the smallest volume of residual cancer survive the longest.[3]

Why does debulking increase survival and improve the results of subsequent chemotherapy in ovarian cancer? First, it may increase blood flow to the remaining tumor masses, increasing the percentage of cells that are well oxygenated, dividing, and susceptible to the effects of cytotoxic agents. Second, the concentration of drug in contact with cancer cells should increase with improved blood supply to the small tumor volumes. Third, removal of tumor bulk may improve the patient's overall physical condition and enhance the activity of her immune system.

Unfortunately, the benefits of debulking surgery in epithelial ovarian cancer have never been demonstrated in a randomized controlled clinical trial comparing it with primary treatment with chemotherapy following initial surgery to document the presence of ovarian cancer.

Is aggressive surgery always needed?

Recently, a number of clinical investigators questioned whether aggressive surgery is appropriate for all patients with advanced ovarian cancer. Some argue that for patients with very advanced disease, in whom surgery is unlikely to leave only small-volume residual cancer, chemotherapy should be given before surgery. In women who respond well to chemotherapy, surgery can be performed subsequently to remove any residual tumor.[11,12] This approach, called "neoadjuvant chemotherapy," is also appropriate for selected patients with a poor performance status, in whom surgery might pose an unacceptably high risk.

ADVANCES IN CHEMOTHERAPY OF OVARIAN CANCER

Based on results of several landmark randomized trials,[13–23] the standard chemotherapy regimen for ovarian cancer has changed substantially during the past decade, and the platinum agents cisplatin and carboplatin have become the cornerstone.[1,3]

Cisplatin-paclitaxel improves survival

In 1996, a multi-institutional study conducted by the Gynecologic Oncology Group demonstrated that the combination of cisplatin and paclitaxel extended both progression-free survival and overall survival in advanced ovarian cancer compared with the previous gold standard of cisplatin and cyclophosphamide (an

Five-year survival of patients with epithelial ovarian cancer, by stage

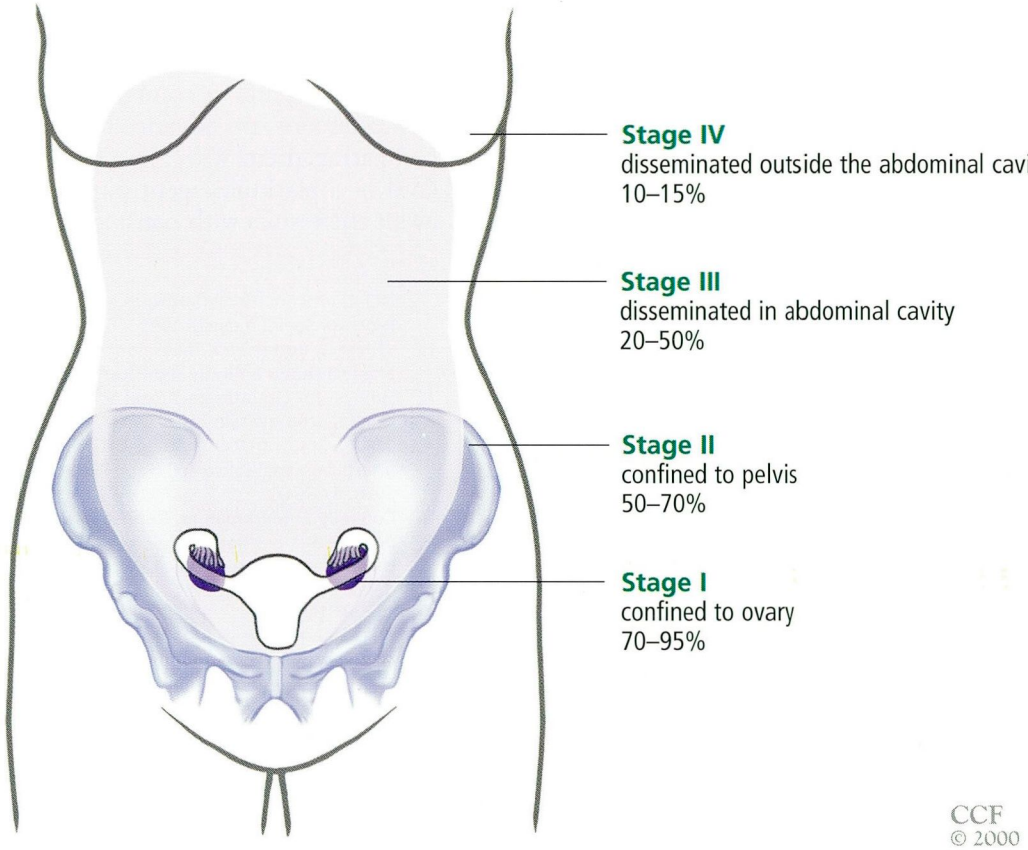

FIGURE 1

alkylating agent).[13] The results of this important trial were recently confirmed by a large randomized study[14,15] conducted at a number of institutions in Canada and Europe.

Carboplatin-paclitaxel less toxic, safe for outpatient therapy

To reduce the toxicity of the standard cisplatin-paclitaxel regimen and develop an outpatient treatment program (paclitaxel must be given as a 24-hour infusion when given with cisplatin[14,16]), researchers examined the combination of carboplatin and paclitaxel.[17,18] Recent trials[19,20] confirmed that an outpatient regimen of carboplatin-paclitaxel given as a 3-hour infusion is as effective, less toxic, and easier to administer than the cisplatin-paclitaxel regimen. On the basis of these data and clinical experience, this combined regimen should be considered the standard of care in chemotherapy of advanced ovarian cancer.

Intraperitoneal vs intravenous delivery

Another important development in ovarian cancer chemotherapy is the use of intraperitoneal cisplatin to treat small-volume residual advanced ovarian cancer.[21–23] Patients with small-volume residual disease are those with no gross residual cancer after initial surgical cytoreduction, or those in whom the largest tumor nodule within the peritoneal cavity is less than 1 cm in diameter. Studies reported that, compared with intravenous delivery of cisplatin, intraperitoneal delivery was associated with an improvement in both progression-free and overall survival.[22,23]

The Gynecologic Oncology Group is currently comparing intraperitoneal vs intra-

venous delivery of cisplatin and paclitaxel in patients with small-volume residual disease. The results should be available within the next 2 to 3 years and may change our approach to the management of this subgroup of patients.

New chemotherapeutic agents

The last several years have also seen the introduction into clinical practice of a number of new cytotoxic agents (eg, topotecan, gemcitabine, oral etoposide, liposomal doxorubicin, vinorelbine, doxetaxel) with demonstrated activity against tumor that is resistant to both platinum agents and paclitaxel. These drugs appear to work via different mechanisms. A number of multi-institutional randomized trials are underway to examine the efficacy of these new agents in combination chemotherapy regimens in advanced ovarian cancer, comparing them with the current gold standard of a platinum agent plus paclitaxel. We await the results with considerable interest.

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