**Epithelial ovarian cancer—EML**

The application sought endorsement of carboplatin, paclitaxel, doxorubicin and etoposide, already listed on the complementary list of the Essential Medicines List, for the treatment of epithelial ovarian cancer. The application also sought the addition of cisplatin and gemcitabine to the core list of the Model List for the same indication.

The application, amended to include details of the Expert Committee’s considerations and decision, is presented in this section.

**Introduction**

Epithelial ovarian cancer is the most common type of ovarian cancer and the most aggressive gynaecological malignancy. Approximately 70% of patients are diagnosed at an advanced stage because of the asymptomatic nature of the disease. Early diagnosis is further hindered by the absence of effective screening tests: serum tumour marker carbohydrate antigen 125 (CA-125), an antigen correlated with breast, lung and gastrointestinal malignancies, cannot adequately be characterized as a screening test because of the overall low incidence of ovarian cancer in the general population and the risk of a false-positive result (1). Diagnosis involves gynaecological examination to identify an adnexal mass, combined with ultrasonography and CA-125, but the gold standard for conclusive diagnosis and staging remains surgical excision and further histological examination of the adnexal mass.

Surgery also provides tumour debulking with the ultimate goal of complete macroscopic tumour resection (optimal cytoreduction) (2). Epithelial ovarian cancer is one of the most sensitive of all solid tumours to cytotoxic drugs: initial response to standard primary treatment, including surgical cytoreduction and adjuvant platinum-based combined chemotherapy, is approximately 80% (3). Five-year survival rate is approximately 43% (4).

**Public health relevance**

Epithelial ovarian cancer is not among the most common human malignancies, but it is a major public health concern because of its disproportionate impact on cancer morbidity and mortality: 238 719 new cases were detected in 2012 (5), an increase in morbidity compared with 225 500 new cases in 2008 (6). The lifetime risk of epithelial ovarian cancer is approximately 0.67% in sporadic cases across all countries, and is somewhat greater in more developed regions (1.01%) (5). Incidence of the disease is lower in developing than in developed countries: the 2012 age-standardized rates in South and North America were 5.8 and 8.1 per 100 000, respectively. The risk of ovarian cancer greatly increases in patients with a familial predisposition (10–40% greater risk than in the general population). The median age at diagnosis for sporadic cancer is 60 years; predisposed patients may be affected earlier,
often in their fifth decade. Age-specific incidence of sporadic disease reaches its peak in women aged 75 years and over.

Despite a statistically significant improvement in treatment results over the last years, ovarian cancer remains the leading cause of gynaecological cancer mortality, with 151,917 ovarian cancer-related deaths registered in 2012 (5). Moreover, mortality is much higher in developing countries, probably as a consequence of the high prevalence of advanced-stage cases and lower level of cancer care.

Nulliparous women and those who have not breastfed are at increased risk for developing ovarian cancer; tubal ligation, oral contraception and African race reduce the risk. Endometriosis is associated with a significantly increased risk of clear-cell, low-grade serous and endometrioid invasive ovarian cancer (7).

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Surgery remains the gold standard for confirming diagnosis and staging ovarian cancer. Laparotomy serves three main purposes in the management of patients with suspected ovarian cancer:

- to confirm histological type of disease;
- to determine the extent of disease (staging), which is critical in determining whether postoperative treatment will be necessary, and to assess prognosis;
- to permit debulking of tumour since patients with optimal cytoreduction (defined as residual tumour of diameter ≤1 cm) have a better prognosis than those with greater amounts of residual disease (8).

Laparoscopy may be used to evaluate a pelvic mass although open surgery is usually preferred when there is high suspicion of malignancy. Histological confirmation of the disease should be made on the basis of biopsies of all suspicious sites relevant for staging, such as omentum, mesentery, liver, diaphragm, pelvic and para-aortic lymph nodes (9, 10).

Surgery

As noted above surgery is important in diagnosis, staging and debulking. Debulking surgery is often done at diagnosis, but can also be performed after three or six cycles of cytoreductive chemotherapy.

Testing

The goal of clinical (preoperative) staging is the confirmation of a malignant adnexal mass, exclusion of another primary tumour, assessment of tumour spread and estimation of possible complications of the disease or further treatment.

Computerized tomography (CT) and magnetic resonance imaging (MRI) are standard imaging methods for tumour evaluation and postoperative surveillance. If CT and MRI cannot be used, ultrasonography becomes the method of choice.
The CA-125 serum level should be assessed. Carcinoembryonic antigen (CEA) assessment is optional; it may be useful to distinguish primary serous tumours from primary mucinous tumours or in differentiating ovarian tumours from ovarian metastases of colorectal cancer. Alpha-fetoprotein and beta-chorionic gonadotropin help to exclude germ cell tumours in women younger than 40 years. Other tests that should be done include blood chemistry for the assessment of renal and hepatic functions (liver enzymes, total bilirubin, albumin and creatinine levels) and complete blood count.

**Administration and care of patients**

Chemotherapy drugs for the treatment of ovarian cancer require peripheral or central venous access. Administration can be performed in either outpatient or inpatient facilities. Antiemetic prophylaxis ideally includes administration of 5HT3-antagonists before the start of chemotherapy. Administration of paclitaxel requires the use of dexamethasone, an H2 blocker, and diphenhydramine to prevent hypersensitivity reactions.

**Intravenous vs intraperitoneal chemotherapy**

Chemotherapy is most often administered intravenously but certain agents are sometimes administered intraperitoneally. Intraperitoneal administration has been associated with a small improvement in survival outcomes (11) but is technically difficult, even in resource-rich settings, and is not generally recommended.

Safety monitoring during chemotherapy requires weekly evaluation of complete blood counts. Patients should regularly visit a medical/general oncologist. Efficacy assessment and follow-up after completion of treatment should be performed using the same methods to evaluate tumour size and spread as were used initially.

**Overview of regimens**

Ovarian cancer is a chemosensitive disease and chemotherapy is therefore one of the most important components of its systemic treatment.

Standard first-line chemotherapy consists of paclitaxel and carboplatin, both administered intravenously every 3 weeks. Patients with early stage IA–IB disease, with low-grade, or well differentiated, adenocarcinoma after adequate staging, require observation only. In the case of intermediate prognosis (stage IA–IB with moderately well differentiated adenocarcinoma after optimal cytoreduction), four cycles of paclitaxel and carboplatin at 3-week intervals are prescribed.

Standard chemotherapy for advanced ovarian cancer (stage IC–IV) includes six cycles of platinum-based regimens, usually paclitaxel and carboplatin or paclitaxel and cisplatin. The paclitaxel/carboplatin combination is as effective as, but less toxic than, paclitaxel/ cisplatin and less complex to administer (12). If taxanes are unavailable, carboplatin or cisplatin can be given as a single agent, but this is not considered optimal therapy.
Standard regimens for first-line therapy

- carboplatin AUC 6 IV infusion on day 1
paclitaxel 175 mg/m² IV infusion on day 1
- cisplatin 75 mg/m² IV infusion on day 1
paclitaxel 175 mg/m² IV infusion on day 1

Second-line therapy for patients with recurrent disease after initial chemotherapy

Approximately 80% of patients diagnosed with ovarian epithelial cancer will relapse after first-line platinum- and taxane-based chemotherapy and may benefit from subsequent therapies (13). Systemic treatment options for patients with recurrent disease are subdivided into three categories according to the platinum-free interval: platinum-refractory – progressing during therapy; platinum-resistant recurrence – progressing within 6 months after completion of platinum-based chemotherapy; and platinum-sensitive – progressing after more than 6 months after completion of platinum-based chemotherapy.

Therapeutic options for second-line therapy include combinations of a platinum compound with paclitaxel, gemcitabine, etoposide or doxorubicin as listed below. All have similar efficacy and the choice will depend on patient status and drug availability. Six cycles of chemotherapy at 3-week intervals is recommended.

Standard regimens for platinum-sensitive relapse (≥6 months)

- carboplatin AUC 5 IV infusion on day 1
paclitaxel 175 mg/m² IV infusion on day 1
- cisplatin 75 mg/m² IV infusion on day 1
paclitaxel 175 mg/m² IV infusion on day 1
- carboplatin AUC 4 IV infusion on day 1
gemcitabine 1000 mg/m² IV infusion on days 1 and 8
- cisplatin 75 mg/m² IV infusion on day 1
etoposide 100 mg orally on days 1–7
- carboplatin AUC 5 IV infusion on day 1
doxorubicin 50 mg/m² IV infusion on day 1

Platinum-refractory and resistant relapse

In patients with platinum-resistant relapse, treatment is focused on quality of life and control of symptoms (14). Monotherapy with different non-platinum agents has similar efficacy; agents such as doxorubicin, liposomal doxorubicin, etoposide, gemcitabine, topotecan and bevacizumab-containing regimens can be used in this situation. Some regimens, such as those including bevacizumab, have shown benefit only in terms of progression-free survival with no evidence supporting overall survival benefit. Extension of life is minimal, and these agents are not proposed for addition to the EML for this indication.
Review of benefits and harms

Benefits

For women with stage IC and above ovarian cancer, clear cell histology or other high-risk features, first-line adjuvant chemotherapy with carboplatin and paclitaxel is recommended on the basis of ICON 1 and EORTC ACTION trials (15, 16). Together, these trials involved more than 900 patients and demonstrated a significant improvement in recurrence-free survival (76% vs 65%; \( P = 0.001 \)) and overall survival (82% vs 74%; \( P = 0.008 \)) at 5 years (17). Benefit was maintained at 10-year follow-up (18). A greater effect of adjuvant chemotherapy was observed in patients who had suboptimal surgery.

A randomized phase III trial compared three and six cycles of adjuvant carboplatin and paclitaxel in early-stage epithelial ovarian carcinoma (19). After three years, recurrence rate following six cycles of therapy was 24% lower than that following three cycles (HR 0.761; 95% CI: 0.51–1.13; \( P = 0.18 \)). The estimated probability of recurrence within five years was lower in the six-cycle group (20.1% vs 25.4%). Overall death rate was similar for both regimens.

Administration of platinum-based regimens in first-line chemotherapy has been shown to improve progression-free survival (PFS) to as much as 18 months and overall survival to 44 months. Median overall survival (OS) has improved from 18–24 months two decades ago to 40–60 months; 5-year OS is currently about 44% (20). There is no benefit from adding a third chemotherapy agent to standard chemotherapy (21).

Patients with platinum-resistant ovarian cancer form a poor-prognosis population, characterized by low response rates (<10%) with short expected OS (14). Administration of doublet chemotherapy has not been shown to improve PFS but does increase toxicity compared with monotherapy with non-platinum agents.

For platinum-sensitive ovarian cancer, carboplatin doublet chemotherapy with paclitaxel or with gemcitabine is now considered the treatment of choice. Compared with conventional platinum-based chemotherapy, paclitaxel plus platinum chemotherapy improved median OS by 5 months (29 vs 24 months) and median PFS by 3 months (13 vs 10 months) in patients with relapsed platinum-sensitive ovarian cancer in the ICON 4 trial (22).

A 2006 inter-group trial (AGO-OVAR, the NCIC CTG, and the EORTC GCG) of 365 patients randomized to receive carboplatin alone or carboplatin with gemcitabine found the doublet regimen significantly improved PFS in patients with platinum-sensitive recurrent ovarian cancer (23). With a median follow-up of 17 months, median PFS was 8.6 months (95% CI: 7.9–9.7 months) for the doublet regimen and 5.8 months (95% CI: 5.2–7.1 months) for carboplatin (HR 0.72; 95% CI: 0.58–0.90; \( P = 0.0031 \)). Response rates were 47.2% (95% CI: 39.9–54.5%) for doublet therapy and 30.9% (95% CI: 24.1–37.7%) for carboplatin alone. No significant difference in OS was observed between treatment arms (HR 0.96; 95% CI: 0.75–1.23); however, the trial was not powered to detect improvement in OS.
The Committee noted that doxorubicin and etoposide have also been associated with small improvements in PFS and OS when used for the treatment of patients with platinum-resistant and platinum-sensitive recurrent disease (24, 25). However, the Committee also noted that these medicines are used infrequently in clinical practice and are not considered to be standard of care.

Harms and toxicity considerations

Common

Patients receiving treatment for ovarian cancer experience common drug toxicity reactions. Most patients suffer haematological toxicity from the medication combination including neutropenia, thrombocytopenia, and anaemia, all of which are typically rapidly reversible upon discontinuation of agents (21, 22). Paclitaxel can cause hypersensitivity reactions in up to 30% of patients and requires premedication to reduce the risk of these reactions. Paclitaxel frequently causes alopecia and peripheral neuropathy, which is often mild and reversible (26, 27). Cisplatin and carboplatin can cause severe, potentially dose-limiting nausea and vomiting requiring pretreatment with anti-emetics.

Serious

In approximately 10-30% of cases, cisplatin causes nephrotoxicity which may result in electrolyte abnormalities, aggressive IV hydration is necessary to reduce this risk (22). Doxorubicin is associated with the risk of congestive heart failure, although the risk is small (<1%) in patients receiving <450–500 mg/m² cumulative dose, as in the regimens above (27).

Recommendations

The Committee considered that combination therapy with carboplatin and paclitaxel is the preferred first-line treatment for the treatment of epithelial ovarian cancer, as it is associated with less toxicity and is easier to administer than cisplatin and paclitaxel. The Committee endorsed the use of already-listed carboplatin and paclitaxel on the complementary list for this indication.

The Committee did not support the specific addition of cisplatin to the Model List for the treatment of epithelial ovarian cancer but considered that cisplatin may be used in circumstances where carboplatin is unavailable.

On the basis of the available evidence, the Committee also recommended the addition of gemcitabine to the complementary list of the Model List of Essential Medicines.

The Committee did not recommend endorsement of doxorubicin or etoposide on the Model List for treatment of epithelial ovarian cancer, noting that – while there is some evidence of benefit in terms of progression-free and overall survival – these medicines are not widely used in clinical practice for this indication and are not considered the current standard of care.