clinical practice guidelines

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Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

Ovarian cancer is the ninth most common cancer in women (excluding skin cancer). It ranks fifth as the cause of cancer death in women. A woman's risk of getting invasive ovarian cancer in her lifetime is about 1 in 71 and the lifetime risk of dying from invasive ovarian cancer is about 1 in 95. In the United States, ~21 550 new cases and 14 600 deaths are estimated annually. There are, however, large variations in the incidence of ovarian cancer in different areas of the world; in the European Union the estimated number of newly diagnosed cases was 42 700 in 2004 with a mortality of 12/100 000 women/year. The majority of these deaths were from ovarian cancer of the serous histological type and around half of women who are diagnosed with ovarian cancer are 60 or older. Ovarian cancer is therefore an important public health issue in Western countries, although >50% of new cases diagnosed every year worldwide occur in developing countries.

Several risk factors have been correlated with ovarian cancer, such as obesity, talcum powder use and certain fertility drugs, but none has been so strongly correlated as poor reproductive history and duration of reproductive career. Early menarche and late menopause seem to increase the risk of ovarian cancer. Another important risk factor for ovarian cancer is genetic predisposition in fact women who carry *BRCA1* or *BRCA2* mutations have an estimated lifetime risk of between 60% and 85% of developing breast cancer, and a lifetime risk of between 26% and 54% of developing ovarian cancer for *BRCA1*, and between 10% and 23% for *BRCA2*. The factors associated with a decreased risk of ovarian cancer are the use of oral contraceptives, breastfeeding, bilateral tubal ligation or hysterectomy, prophylactic oophorectomy.

pathology

traditional pathological approach

Approximately 90% of primary malignant ovarian tumours are epithelial (carcinomas). Most are thought to arise from the ovarian surface epithelium or Mullerian derivatives including the distal Fallopian tube; peritoneal tumours of ovarian type are staged as ovarian primaries. The World Health Organization (WHO) classification of ovarian tumours recognizes six major histotypes (serous, mucinous, endometrioid, clear cell, transitional cell and squamous). Tumours of each type are further subdivided into three prognostically relevant categories (benign, malignant and intermediate, the latter known as tumours of borderline malignancy or low malignant potential and atypical proliferative tumours). According to their architectural features, carcinomas are classified into three grades corresponding to percentage (<5%, 5%–50% and >50%) of solid growth on glandular and papillary component, by the FIGO (International Federation of Gynecology and Obstetrics) system. At present, it is recognized that a universal, multifactorial grading system for all ovarian carcinomas is difficult to apply.

recent advances

With the recognition of relevant subtypes and refinement of prognostic criteria, there is now evidence that ovarian cancer represents a group of distinct entities with distinct types of carcinogenesis, which should benefit from a more specific approach.

Overall, the most significant advances are the following:

- Mucinous tumours consist of two subgroups, the so-called endocervical-like (seromucinous or Mullerian) mucinous tumours, usually in the borderline category and similar to borderline serous tumours, and the intestinal type, the latter being the more common. In this subtype, pathological studies

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are very important in distinguishing between metastatic carcinoma from the upper gastrointestinal tract (including biliary tract), pancreas and cervix, and primary ovarian mucinous tumour.
- Borderline tumours are considered precursors of serous carcinoma following the identification of low-grade serous carcinomas, which account for those carcinomas occurring in association with or in the follow-up of borderline tumours. Borderline tumours can also less frequently be mucinous, and rarely endometrioid.
- In high-grade serous carcinomas, grading is no longer considered reproducible and prognostically useful following the recognition that low-grade serous carcinoma is a distinct type of tumour.

conventional high-grade serous carcinoma and low-grade serous carcinoma

Approximately 80%–85% of all ovarian carcinomas in Western countries are serous. Up to 95% of patients with FIGO stage III–IV disease have serous carcinomas, while FIGO stage I serous carcinomas are very uncommon.

Serous carcinomas typically show papillary, micropapillary architecture and solid growth with typical slit-like spaces; glandular, cribriform and trabecular features, which are more common in non-serous carcinomas, may also occur. Recent pathological and molecular studies suggest that the secretory epithelium cells of the Fallopian tube may be the site of origin for high-grade serous ovarian tumours in the hereditary ovarian cancer setting.

The rare low-grade serous carcinomas are characterized by low grade of cell atypia and low mitotic activity in the range of epithelial changes of borderline tumours.

endometrioid and clear cell carcinoma

Endometrioid carcinomas have decreased in prevalence, accounting for the second most common ovarian carcinoma subtype (~10% of all ovarian carcinomas). Clear cell carcinomas are ~5% of all ovarian carcinomas and are particularly common only in Japanese women. Most endometrioid and clear cell carcinomas are FIGO stage I or II and endometrioid carcinoma is the most common tumour in FIGO stage I.

transitional cell carcinoma

Carcinomas with transitional-like features are quite common; however, most are papillary high-grade tumours with histological features and immunofenotype (expression of WT1 and p53) in the range of serous carcinomas.

other carcinomas

A group of tumours designated as Mullerian mucinous or endocervical-like mucinous or seromucinous or mixed epithelial neoplasms with a mucinous component characteristically demonstrate the low-power appearance of serous borderline tumours. The lesional cells are a mixture of endocervical-type cells with apical mucin (but not goblet cells), ciliated cells and so-called indifferent cells. These tumours typically show an association with endometriosis. Many undifferentiated carcinomas of ovarian surface epithelium origin behave as high-grade serous carcinomas.

molecular correlation and pathogenetic approach

The subclassification proposed by Kurman, based on pathology and genetics, consists of two groups designated type I and type II. Type I tumours include those that arise from well-characterized precursor lesions, specifically borderline tumours; some have a variable behaviour (mucinous, endometrioid and clear cell carcinomas) while others are slowly growing neoplasms (low-grade serous carcinomas). Type I tumours show a number of different mutations (including KRAS, BRAF, PTEN and β-catenin) and are relatively genetically stable. Low-grade serous carcinomas and their precursor lesions, serous borderline tumours, are characterized by mutually exclusive sequence mutations in KRAS, BRAF and ERBB2 oncogenes. Mutations of KRAS and BRAF seem to occur very early in the development of low-grade serous borderline tumours, since the same KRAS and BRAF mutations detected in serous borderline tumours were present in the cystadenoma epithelium adjacent to the serous borderline component. Mutations of KRAS and BRAF have been reported in ~10% of endometrioid carcinomas, mutation of PTEN in another 20%. Similar molecular genetic alterations, including loss of heterozygosity at 10q23 and PTEN mutations, have been observed in endometriosis, atypical endometriosis and ovarian endometrioid carcinoma in the same specimen. Mutations in KRAS and PTEN instability have been reported in clear cell carcinoma.

Type II tumours, on the contrary, are high grade, biologically aggressive tumours that do not have a recognized precursor lesion and are thought to arise *de novo* from coelomic epithelium; the prototype is serous carcinoma: included in this group are high-grade transitional carcinomas, malignant mixed mesodermal tumours (MMMTs) and undifferentiated carcinomas. Type II tumours show considerable genetic instability and TP53 mutations, while the mutations characteristic of type I tumours are not detected. Hereditary cancers with BRCA1 and BRCA2 mutations belong to type II tumours.

diagnosis

The most frequent symptoms are abdominal discomfort or vague pain, abdominal fullness, bowel habit changes, early satiety, dyspepsia and bloating. The presence of a pelvic mass at clinical evaluation is an important sign of possible ovarian cancer. Occasionally, patients may present with bowel obstruction due to intra-abdominal masses or shortness of breath due to pleural effusion. In early stage disease, the patient may complain of irregular menses if she is premenopausal; if a pelvic mass is compressing the bladder or rectum, the patient may report urinary frequency and/or constipation. Occasionally, the patient may perceive lower abdominal distention, pressure or pain, such as dyspareunia; acute symptoms, such as a pain secondary to rupture or torsion, are unusual.

In advanced stage disease, patients most often have symptoms related to ascites and abdominal distension due to masses. The symptoms include abdominal distention, bloating, constipation, nausea, anorexia or early satiety. In stage IV disease, shortness of breath due to pleural effusion is also reported. If nodal metastases are present, enlarged inguinal,

supraclavicular and axillary nodes may be palpated. The serum CA125 level has been widely used as a marker for a possible epithelial ovarian cancer in the primary assessment of a suspect adnexal mass. In this setting, false-positive results may derive from several conditions, in particular those associated with peritoneal inflammation, such as endometriosis, adenomyosis, pelvic inflammatory disease, menstruation, uterine fibroids or benign cysts. In a retrospective analysis of serum samples from 5550 women who were enrolled in a population-based registry in Sweden, 175 women had elevated CA125 values. Ovarian cancer was ultimately diagnosed in six of these women and also developed in three women with normal CA125 values. The specificity of the test was 98.5% for women over the age of 50 years but was lower (94.5%) for those who were younger than 50 (i.e. it had a low positive predictive value). As compared with women with an elevated CA125 value in whom ovarian cancer was not diagnosed, the women who ultimately were found to have ovarian cancer were more likely to have progressive elevation of the CA125 value over time.

Transvaginal ultrasonography is often included among the procedures for the evaluation of a pelvic mass. Features highly suggestive of advanced ovarian cancer are the presence of a complex ovarian mass, with both solid and cystic components, sometimes with internal echoes and/or septations, ascites or evidence of peritoneal metastases in the presence of an ovarian mass. The use of multimodal screening (serum CA125 measurement and ultrasound imaging) for early detection of ovarian cancer seems to be effective. In a large randomized controlled trial a total of 202 638 post-menopausal women (aged between 50 and 74 years) were randomly assigned to no treatment, annual CA125 screening with transvaginal ultrasound scan as a second-line test or annual screening with transvaginal ultrasound alone. The study showed that the use of CA125 with ultrasound scan has a higher specificity than transvaginal ultrasound alone to detect primary ovarian and tubal cancers. Despite these promising results, multimodal screening is not considered yet the gold standard for early detection of ovarian cancer. Further randomized controlled studies are needed to demonstrate the impact of multimodal screening on survival of patients with ovarian cancer. Other imaging techniques, such as magnetic resonance imaging (MRI) or positron emission tomography (PET), may provide additional information but are not routinely necessary in preoperative evaluation. The goal of imaging in ovarian cancer detection is to expeditiously distinguish benign adnexal lesions from those requiring further pathological evaluation for malignancy. For lesions indeterminate on ultrasound, MRI increases the specificity of the imaging evaluation, thus decreasing benign resections. CT is useful in diagnosis and treatment planning of advanced cancer. Although FDG-avid ovarian lesions in postmenopausal women are considered suspicious for malignancy, PET/CT is not recommended for primary cancer detection because of high false-positive rates.

staging and risk assessment

Surgical staging requires a laparotomy by a midline incision for adequate exposure and careful examination of the abdominal cavity according to the FIGO guidelines (Table 1). If disease

Table 1. Staging of cancer of the ovary

Stage I	Growth limited to the ovaries
IA	Growth limited to one ovary; no ascites present containing malignant cells. No tumour on the external surface; capsule intact
IB	Growth limited to both ovaries; no ascites present containing malignant cells. No tumour on the external surfaces; capsules intact
IC[a]	Tumour either stage IA or IB, but with tumour on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
IIA	Extension and/or metastases to the uterus and/or tubes
IIB	Extension to other pelvic tissues
IIC[a]	Tumour either stage IIA or IIB, but with tumour on surface of one or both ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings
Stage III	Tumour involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive regional lymph nodes. Superficial liver metastases equal stage III. Tumour is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum
IIIA	Tumour grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologic proven extension to small bowel or mesentery
IIIB	Tumour of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative
IIIC	Peritoneal metastasis beyond the pelvis >2 cm in diameter and/or positive regional lymph nodes
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equals stage IV

[a]In order to evaluate the impact on prognosis of the different criteria for allotting cases to stage IC or IIC, it would be of value to know whether rupture of the capsule was spontaneous, or caused by the surgeon and whether the source of malignant cells detected was peritoneal washings or ascites.
Reprinted with permission by the International Federation of Gynecology and Obstetrics (FIGO): Odicino F, Pecorelli S, Zigliani L, Creasman WT. History of the FIGO cancer staging system. Int J Gynecol Obstet 2008; 101: 205–210

appears confined to the ovary, staging procedures include biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum, complete or selected lymphadenectomy of the pelvic and para-aortic lymph nodes, infracolic, omentectomy, four washings of the peritoneal cavity (diaphragm, right and left sides of the abdomen and pelvis); total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO); appendectomy for mucinous tumours.

Surgical staging studies of apparent early stage ovarian cancers have confirmed that up to 22% of patients will have their disease upstaged. Young *et al.* performed a systematic restaging in 100 consecutive patients operated elsewhere and initially assessed as having stage I or II ovarian cancer. In 31 (31%) of 100 patients, the stage was higher, and 23 (77%) of the 31 patients had stage III disease. Sites of unsuspected disease were most likely to be pelvic peritoneum, ascites fluid, other pelvic tissues, para-aortic nodes and diaphragm.

The importance of performing pelvic and para-aortic lymph node dissection is due to the high rate of nodal involvement in patients with apparent stage I or II. Cass and colleagues showed in 96 patients with gross disease confined to one ovary, that 15% had microscopically positive lymph nodes. Among these patients, 50% had positive pelvic nodes, 36% had positive para-aortic node and both were positive in 14% of the cases. All these patients were grade 3. In the case of advanced disease retroperitoneal dissection is not routinely performed and the prognostic benefits remain controversial. Benedetti Panici et al. conducted a randomized clinical trial to determine the impact of systematic aortic and pelvic lymphadenectomy on progression-free (PFS) and overall survival (OS) comparing with resection of bulky nodes only in stage IIIB–C and IV epithelial ovarian carcinoma patients. The authors demonstrated that systematic lymphadenectomy improved PFS but not OS [I].

Staging should be carried out by an appropriately trained surgeon with experience in the management of ovarian cancer. Most general surgeons are unfamiliar with retroperitoneal anatomy in the pelvis, particularly around the side wall and blood vessels. The evidence demonstrates that the performance of an adequate surgical staging is most likely to be not 'correctly' performed by a general surgeon (65%) rather than a general gynaecologist (48%).

Primary cytoreductive surgery is the standard approach to initial treatment of patients with advanced ovarian cancer. Theoretically, there are good reasons to believe that tumour debulking will increase survival. In fact, tumour reduction before chemotherapy may synchronize cell division, improve drug availability to metastases, reduce the number of cycles of chemotherapy required to eradicate residual disease and diminish development of subsequent drug resistance. Bristow et al. evaluated 81 studies involving 6885 patients and demonstrated that each 10% increase in the number of patients receiving maximal cytoreduction was associated with a 5.5% increase in median survival. Furthermore, the prognosis of patients with suboptimal tumour debulking surgery remains poor. In patients in whom optimal debulking is not feasible, interval debulking surgery should be considered; in fact several retrospective studies have demonstrated a decreased morbidity with acceptable survival rate. In 1995, the Gynecological Cancer Cooperative Group (GCG) of the European Organization for Research and Treatment of Cancer (EORTC) showed in a prospective randomized study that interval debulking surgery significantly lengthens PFS and OS.

Approximately 15% of epithelial ovarian cancer is diagnosed as stage IV disease. Overall, median survival for patients with stage IV disease is ~15–23 months with an estimated 5-year survival of 20%. A retrospective analysis of 360 patients with stage IV who underwent primary surgery followed by chemotherapy [six cycles of intravenous (i.v.) platinum/paclitaxel] showed that patients with microscopic residual tumour after surgery had the best outcome whereas patients with 0.1–1.0 cm residual disease and patients with 1.1–5.0 cm residual disease had similar PFS and OS. Furthermore, ultra-radical cytoreduction might be justified in selected cases if microscopic residual tumour can be achieved.

primary treatment

early disease: FIGO stage I–IIa

In patients with disease apparently confined to the pelvis and absence of extra-abdominal metastatic disease, surgical staging is essential to provide better prediction of outcome and it is an independent prognostic factor for survival influencing ongoing management.

Total abdominal hysterectomy and BSO with omentectomy, peritoneal washing, peritoneal biopsies, evaluation of the entire abdominal cavity and retroperitoneal assessment that involves both the pelvic and para-aortic area should be performed.

In selected patients who desire to preserve their childbearing potential, unilateral salpingo-oophorectomy with adequate staging may be performed after proper counselling.

With the advent of minimally invasive surgical techniques, surgeons are now able to perform all the necessary procedures for comprehensive surgical staging by laparoscopy or robotics, including laparoscopic pelvic and para-aortic lymphadenectomy and omentectomy. Large studies evaluating disease-free interval and OS are needed before concluding that laparoscopic staging of early stage ovarian cancer is preferable to laparotomy.

prognostic factors

Classic clinical and pathological prognostic factors, such as degree of differentiation, FIGO stage, histological type, large volume of ascites, rupture before surgery, extracapsular growth and age of the patient, have been identified by multivariate analyses as independent prognostic factors in epithelial ovarian cancer.

Vergote et al. in a large series of patients with early stage ovarian cancer showed that the degree of differentiation was the most powerful prognostic indicator of disease-free survival. This was followed by rupture before surgery, rupture during surgery bilaterality of the tumour and age.

Based on these prognostic factors, optimally staged tumours can be classified as at low, medium or high risk for recurrence.

Low risk includes stage IA–IB grade 1 tumour; medium risk includes stage IA and IB grade 2; high risk includes stage IC all grades, IB or IC grades 2 and 3, clear cell histology.

chemotherapy

Adjuvant chemotherapy for early stage ovarian cancer remains a controversial topic.

A recent meta-analyses of 5 large prospective clinical trials (4 of 10 with platinum-based chemotherapy) showed that chemotherapy is more beneficial than observation in patients with early stage ovarian cancer. The patients who received platinum-based adjuvant chemotherapy had better OS [hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.53–0.93] and PFS (HR 0.67; 95% CI 0.53–0.84) than patients who did not receive adjuvant treatment. Even though two-thirds of the patients included in the two major studies were suboptimally staged, some benefit for chemotherapy in optimally staged patients cannot be excluded. Therefore, it seems wise to conclude that adjuvant chemotherapy should be offered not only to suboptimally staged patients but also to optimally staged medium or high-risk patients.

The optimal duration of treatment remains controversial; in fact only one randomized trial (GOG 157) showed that six cycles of carboplatin and paclitaxel were not associated with longer PFS and OS, but with a significantly greater toxicity than three cycles.

Therefore, based on meta-analysis data, we recommend six cycles of single-agent carboplatin as adjuvant treatment in patients with intermediate and high-risk early stage ovarian cancer.

Advanced disease; FIGO stages IIb–IIIc

Stage IIb were included in the advanced stage group because, according to Figo classification, ovarian cancer involves other pelvic tissues with a consequent worsening of prognosis; the reported 5-year survival rate is from 71%–90% in early to 65% in Figo stage IIb.

The standard initial treatment of advanced ovarian cancer consists of cytoreductive surgery followed by a combination platinum-based chemotherapy.

Since 1986 the threshold of ≤1 cm residual disease in greatest dimension has been used to define 'optimal' cytoreduction; an additional survival advantage of cytoreduction to no visible residual disease has been recently reported.

A literature review showed that patients with optimal cytoreduction had a median survival of 39 months as compared to that of 17 months of patients with suboptimal residual disease.

Several studies have consistently shown that specialized surgeons, namely gynecological oncologists, are more likely to perform optimal surgery than general surgeons.

If initial maximal cytoreduction is not carried out, interval debulking surgery (IDS) should be considered in patients responding to chemotherapy or with stable disease [II, B]. IDS should ideally be carried out after three cycles of chemotherapy, followed by three further cycles of the same chemotherapy [III].

chemotherapy

After surgical cytoreduction, the treatment of choice for patients with advanced epithelial ovarian cancer is platinum-based chemotherapy.

Since 1996 the combination of platinum plus paclitaxel has been the standard treatment; in fact the GOG 111 study demonstrated statistically significant outcome advantages for the combination of cisplatin plus paclitaxel compared to the standard regimen of cyclophosphamide plus cisplatin in patients with previously untreated advanced stage III and IV disease. Subsequently, cisplatin was replaced by carboplatin, in view of the GOG 114 results, in which carboplatin, compared with cisplatin, showed equivalent outcomes with less toxicity and better administration [I].

Long-term follow-up in the GOG 111 and OV.10 studies demonstrated PFS in only 18% of patients at 6 years. Efforts to improve these poor long-term outcomes have resulted in a variety of experimental strategies, such as the addition of a third, potentially non-cross-resistant, cytotoxic agent to a platinum/taxane doublet in various schedules.

The largest phase III Gynecologic Cancer Intergroup (GCIG) trial (GOG 0182-ICON 5) enrolled 4312 patients into a 5-arm protocol. Each arm included eight cycles of triplet (carboplatin–paclitaxel–gemcitabine and carboplatin–paclitaxel–liposomal doxorubicin), or sequential-doublet chemotherapy, which provided a minimum of four cycles with the experimental treatments (carboplatin–topotecan and carboplatin–gemcitabine) while maintaining at least four cycles with carboplatin and paclitaxel, or eight cycles of standard treatment (carboplatin–paclitaxel). There was absolutely no statistically significant superiority or clinically useful benefit associated with the three drugs compared with the control arm [I].

Currently, there are no data to recommend any new two- or three-drug combination and carboplatin–paclitaxel still remains the treatment of choice.

Three randomized trials analysed the impact of the duration of chemotherapy (i.e. number of cycles) on OS. None of these studies demonstrated a difference in median survival time, but longer durations were associated with more toxicity, expecially neuropathy. These studies were the basis for the current rationale for six cycles of treatment as the convention.

Epithelial ovarian cancer arises from the epithelial surface of the ovary with intra-abdominal spread to the peritoneal cavity confined to the abdomen.

The intraperitoneal (IP) administration of chemotherapy offers the possibility of targeting therapy to the site of disease while minimizing systemic toxicities. The result of the GOG 172 study, which prompted the NCI announcement in January 2006, showed that IP therapy was associated with longer survival in surgically treated optimal ovarian cancer patients added to i.v. therapy as compared with i.v. therapy alone (65.6 versus 49.7 months of median survival with a 21.6% reduction in death). However, the study raised concern about IP therapy's toxicity and tolerability, since less than half of patients completed the planned experimental treatment (42% of 205 eligible patients).

A recent meta-analysis showed that the hazard ratio for PFS of IP cisplatin as compared with i.v. treatment regimens is 0.792 (95% CI;: 0.688–0.912; $P = 0.001$), and the HR for OS is 0.799 (95% CI 0.702–0.910; $P = 0.0007$). These findings support the incorporation of an IP cisplatin regimen in the front-line treatment of stage III, optimally debulked ovarian cancer. The trade-off between survival and tolerability sets the stage for a future large intergroup phase III trial evaluating IP therapy in first-line treatment of advanced ovarian cancer [I].

treatment of recurrent disease

Appropriate salvage therapy is based on the timing and nature of the recurrence and the extent of prior chemotherapy. Surgical resection should be considered in platinum-sensitive patients with prolonged treatment free-interval (e.g. >24 months), especially with isolated recurrence and good performance status. A recent meta-analysis showed that one of the most important predictors of survival in patients undergone secondary cytoreduction is the complete cytoreduction; in fact, each 10% increase in the proportion of patients undergoing complete cytoreductive surgery was associated with a 3.0 month increase in median cohort survival time. However, the role of aggressive secondary surgery is only supported by retrospective or prospective non-randomized studies; randomized trials are clearly needed to strongly support the advantages of secondary surgery. In general, patients who progress during treatment with platinum are considered to have 'platinum-refractory' disease, patients who develop recurrence <6 months from the completion of first-line platinum chemotherapy are considered to have 'platinum-resistant' disease and those with an interval >6 months 'platinum-sensitive' disease.

Patients experiencing a durable response to platinum induction chemotherapy have a high probability of responding again to platinum-containing compounds. The choice between cisplatin and carboplatin should be based on the agent used in previous therapy, its tolerability and residual toxicity. In order to determine whether the combination carboplatin and paclitaxel should be used at first relapse after platinum-based chemotherapy, two pragmatic trials were designed. ICON4 and OVAR 2.2 were two parallel randomized trials comparing a minimum of six cycles of platinum chemotherapy versus paclitaxel plus platinum in 802 patients relapsing after platinum-based chemotherapy (almost 50% of the patients received platinum–paclitaxel combination) with a treatment-free interval of >6 months (OVAR 2.2) or >12 months (ICON4). The HR for progression was 0.77 and the HR for survival is 0.77 in favour of paclitaxel–platinum combination ($P = 0.006$). There was no evidence that the effect was larger or smaller in any subgroups (randomization group, time to relapse, number of previous lines of chemotherapy, type of prior chemotherapy, age and performance status). These results suggest that the combination improves survival and PFS in patients with 'platinum-sensitive' relapsed ovarian cancer compared with platinum alone [I].

In general, ovarian cancer patients relapsing after first-line platinum–paclitaxel therapy are at risk of significant neurotoxicity when retreated with the same regimen within up to 12 months from the end of first chemotherapy due to cumulative neurotoxicity of both carboplatin and paclitaxel.

The frequency of clinically significant residual neurotoxicity after first-line chemotherapy was part of the rationale for evaluating an active platinum-based combination not associated with this toxic effect. The AGO-OVAR study showed that there was a significant improvement in PFS and response rate without a worsening of quality of life in 356 platinum-sensitive patients who received six courses of gemcitabine and carboplatin combination versus carboplatin alone. PFS in the combination arm and in the single-agent arm was, respectively, 8.6 months (95% CI 7.9–9.7) and 5.8 months (95% CI 5.2–7.1) ($P = 0.0031$); response rate was 47.2% in the combination arm and 30.9% in the single-agent arm. No statistically significant differences in OS were observed.

A multicentre phase III study has been recently presented at the annual meeting of the ASCO comparing efficacy and safety of carboplatin–pegylated liposomal doxorubicin and carboplatin–paclitaxel in 976 relapsed platinum-sensitive ovarian cancer patients. The trial showed non-inferiority of the experimental arm in terms of PFS (11.3 months versus 9.4; HR= 0.821, 95% CI 0.72–0.94; $P = 0.005$) with lower rates of severe and long-lasting toxicity. This treatment could become the new standard in patients with similar disease characteristics.

Salvage chemotherapy in platinum-refractory patients typically results in low response rates and short survival (C). Rechallenge with platinum-based treatments produces a response rate of ∼10%, while the response rate of drugs with antitumour activity in paclitaxel–platinum-refractory disease (topotecan, docetaxel, oral etoposide, liposome encapsulated doxorubicin, gemcitabine, ifosfamide and hexamethylmelamine) is ∼10%. Since the achievement of durable response is rare and cure almost impossible, the main goal of salvage therapy in this group of patients is palliation; therefore, particular attention should be paid to the side-effects of the drugs used. Patients with good performance status and motivated to receive further treatment should be considered for experimental trials with new drugs.

Palliative secondary surgery should be considered to relieve intestinal obstruction in patients who have failed two or more chemotherapy regimens. The criteria for selection of patients for palliative surgery are categorized according to the presumptive estimate of duration of survival, the overall medical status and performance status, presence of ascites, the will to live, presence of focal disease and a suspicion of local obstruction where a bypass or local resection might be feasible.

follow-up

Follow-up after primary therapy in ovarian cancer is poorly defined. History, physical examination including pelvic examination every 3 months for 2 years, every 4 months during the third year and every 6 months during years 4 and 5 or until progression is documented.

The serum assay of CA125 during chemotherapy is used to evaluate the response to the treatment. According to GCIG criteria, progression or recurrence based on serum CA125 levels is defined on the basis of a progressive serial elevation of serum CA125. Elevated values must be confirmed by two separate measurements obtained at least 1 week apart. CA125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not assessable by CA125 if they have received mouse antibodies or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

The serum assay of CA125 is an adequate toll for the follow-up of responders after the completion of chemotherapy since it has been shown to be predictive of ovarian cancer relapse.

With early detection of recurrence, patients often begin treatment before symptoms manifest themselves, but the data available on the efficacy of this procedure are not conclusive. At ASCO 2009 the results of a large phase III randomized study, evaluating whether there were clinical benefits from the early start of treatment, based on increased CA125 antigen, versus a delay of treatment up to the onset of clinical manifestations of the disease, were presented. The study involved 527 patients in complete remission after first-line platinum-based chemotherapy and with normal CA125 level at study entry. Patients randomized to immediate chemotherapy started second-line treatment 4.8 months earlier and third-line treatment 4.6 months earlier than the patients in the delayed-therapy group. With a median follow-up of 49 months and 351 deaths, there was no evidence of difference in OS between immediate and delayed treatment (HR = 1.01; 95% CI 0.82–1.25; $P = 0.91$). Quality of life was lower in the early-treatment group, presumably because this group was exposed to more extensive chemotherapy and had a longer duration of treatment.

The conclusions were that there is no benefit from early detection of relapse by routine CA125 measurement and that, even if CA125 rises, chemotherapy can be delayed until signs or symptoms of tumour recurrence [I]. However, it is important to offer women informed choices in follow-up and keep in mind that a potentially resectable occult macroscopic recurrence can be signalled by a CA125 rise.

CT scans should be performed if there is clinical or CA125 evidence for progressive disease. However, from data in the literature, PET-CT scans seem to be superior to CT scans in detecting more sites of tumour, especially nodal, peritoneal and subcapsular liver disease. If a patient is considered for surgery, PET scan allows a more accurate selection of cases potentially candidates for secondary surgery.

note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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