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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 and epidemiology

The estimated number of new ovarian cancer cases in Europe in 2012 was 65 538 with 42 704 deaths [1]. There is variation in the incidence rate across the continent with a higher incidence in northern European countries. In the USA, there were ∼20 400 newly diagnosed cases and 14 400 deaths in 2009 [2]. Ovarian cancer is the fifth most common type of cancer in women and the fourth most common cause of cancer death in women. The estimated lifetime risk for a woman developing ovarian cancer is about 1 in 54.

Ovarian cancer is predominantly a disease of older, postmenopausal women with the majority (>80%) of cases being diagnosed in women over 50 years. The exact cause of ovarian cancer remains unknown but many associated risk factors have been identified. A woman's reproductive history appears to contribute significantly to her lifetime risk of ovarian cancer. Those women who have had multiple pregnancies have a lower risk than those with fewer pregnancies, who in turn have a lower risk than nulliparous women. Early menarche and late menopause also seem to contribute to a greater risk of ovarian cancer, while use of the oral contraceptive pill, tubal ligation, breastfeeding and suppression of ovulation offer protection against ovarian cancer. All of these risk factors point to ovulation being correlated with the development of ovarian cancer. Further risk factors are obesity and possibly the use of talcum powder.

Family history plays a very important role in the development of ovarian cancer, although in a recent study 44% patients with high-grade serous ovarian cancer and a germline BRCA mutation did not report a family history of cancer [3]. Women with a first-degree relative have more than a twofold increase in risk of ovarian cancer compared with women with no family history. However, only 10% of ovarian cancer cases have an identifiable genetic mutation, e.g. the known susceptibility genes BRCA 1 and BRCA 2. An inherited BRCA 1 mutation confers a 15%–45% lifetime risk of developing ovarian cancer and ≤85% risk of developing breast cancer. A BRCA 2 mutation increases the lifetime risk of ovarian cancer to 10%–20% and breast cancer risk of ≤85%. Women with hereditary ovarian cancer tend to develop the disease ∼10 years earlier than women with non-hereditary ovarian cancer. There are no clear guidelines for referral of ovarian cancer patients for testing. Referral is made on the basis of a family history and ethnic background. The importance of identifying BRCA mutations has increased as, in addition to risk-reducing surgery and surveillance for breast cancer in the patient and in family members, there are new treatments emerging specifically for BRCA-related cancers.

pathology

The majority of cases of ovarian cancer are of epithelial origin (∼90%). The World Health Organisation histological typing of epithelial ovarian tumours recognises the following distinct subtypes [4]:

- serous
- endometrioid
- clear cell
- mucinous
- Brenner (transitional cell)
- mixed epithelial tumours
- undifferentiated
- unclassified

Clinical trials have demonstrated that the subtype has prognostic importance [5] [I]. Grade is an additional prognostic determinant and a number of grading systems currently exist

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which are derived from reviewing the following tumour characteristics: architectural features, mitotic counts and nuclear atypia. Based on these, a grade of 1–3 is most commonly assigned [6]. There is no single universally accepted grading system. Some use a two-tier staging [7]; moreover, it is being recognised increasingly that different grading systems for different histological subtypes should be employed. The complexity of subclassification below and its affect on treatment choice underline the importance of the role of an expert in gynaecological pathology in typing tumours.

serous carcinomas

Invasive serous carcinomas are the most common histological type accounting for up to ~80% of advanced ovarian cancers. In recent years, convincing data have been presented that high-grade serous and low-grade serous ovarian cancers are two distinct disease entities [8, 9]. Tumours with mild to moderate cytologic atypia and low mitotic rates are classified as low-grade, whereas patients with severe cytologic atypia and high mitotic rates are considered high-grade serous tumours. There are also distinct mutations present in each type, and the cell of origin may also be different, as discussed in the next section. Clinically, women with low-grade serous tumours, which account for ~10% of serous cancers tend to present at a younger age and have a longer survival compared with women with high-grade tumours [10]. There is an increasing realisation that low-grade serous tumours do not respond to traditional chemotherapy regimens [11] and that alternative approaches are required particularly for the treatment of recurrent tumours.

endometrioid

The majority of endometrioid ovarian cancers are usually early stage (stage 1) and low grade. The prevalence of endometrioid ovarian cancers has decreased in recent years, likely due to better pathological diagnosis, and currently they account for ~10% of ovarian cancers. Endometriosis and in particular endometriotic cysts have been implicated as putative precursor lesions to endometrioid ovarian cancer. ARID1A mutations have been detected in endometriotic cysts and in endometrioid ovarian cancer, suggesting a causative role [12].

clear-cell cancers

Clear-cell cancers account for ~5% of ovarian cancers, although the incidence varies worldwide. Japanese women develop clear-cell ovarian cancers more commonly. The prognosis for stage 1 clear-cell cancers is relatively good. However, advanced stage clear-cell cancers have a worse prognosis than serous ovarian cancers as the tumours tend to be resistant to the standard chemotherapeutic agents used in ovarian cancer. Clear-cell cancers are also strongly associated with endometriosis and a significant proportion carry ARID1A mutations [12].

transitional carcinoma

Primary ovarian transitional carcinomas are rare but carcinomas with transitional features are quite common. The majority of the latter are variants of high-grade serous carcinomas and exhibit WT1 positivity.

other carcinomas

Mixed carcinomas are diagnosed when a tumour consists of more than one histological type and the minor component forms >10%. Undifferentiated carcinomas are rare and are likely to represent one end of the high-grade serous spectrum [13].

borderline tumours (tumours of low malignant potential)

Borderline tumours comprise about 10%–15% of ovarian tumours and do not fit into the category of benign or malignant. As most ovarian tumours are serous in origin, borderline serous tumours are the most common type but borderline mucinous and endometrioid tumours also occur. Borderline serous tumours form part of the spectrum of low-grade serous cancers. They are managed primarily by surgery and respond poorly to chemotherapy.

molecular pathogenesis

Ovarian cancer is recognised as a heterogeneous disease, and in the last few years a dualistic model for the pathogenesis of this disease has emerged which divides epithelial tumours into type 1 and type 2 ovarian carcinomas. This classification is not intended to replace histological subtypes but provides a parallel terminology pertaining to the broad mechanism of cancer development [13]. Type 1 cancers tend to be low-grade and indolent tumours and include low-grade serous, endometrioid, mucinous, clear-cell and malignant Brenner tumours. These tumours are characterised by mutations of KRAS, BRAF, ERBB2, PTEN, PIK3CA and ARID1A and are relatively genetically stable. These mutations occur early in the evolution of type 1 ovarian tumours and are also observed in borderline tumours and endometriosis. A stepwise sequence of tumour development is now well recognised from benign precursor lesions (e.g. borderline tumour) to malignant lesions in type 1 cancers. Conversely, there is no clear precursor lesion for type 2 cancers. These are high-grade, aggressive tumours comprising high-grade serous, high-grade endometrioid, malignant mixed mesodermal tumours and undifferentiated tumours. Type 2 tumours are very frequently associated with TP53 mutations, and one landmark study found that 97% of high-grade serous cancers were associated with a TP53 mutation. Approximately 20% of these tumours also carried a BRCA1/2 mutation due to a combination of germline and somatic mutations [14].

In recent years, accumulating evidence has shown that the majority of high-grade serous ovarian and peritoneal tumours originate in the fimbria of the fallopian tube (serous tubal intraepithelial carcinoma) [15, 16]. These malignant cells then metastasise to the ovaries and the peritoneal cavity.

diagnosis

Patients with ovarian cancer confined to the ovary may have few or no symptoms, making clinical diagnosis of early ovarian cancer more difficult. Symptoms are most commonly seen with advanced disease. Recognised symptoms of all stages include abdominal or pelvic pain, constipation, diarrhoea, urinary frequency, vaginal bleeding, abdominal distension and fatigue.

In advanced ovarian cancer, ascites and abdominal masses lead to increased abdominal girth, bloating, nausea, anorexia, dyspepsia and early satiety. Extension of disease across the diaphragm to the pleural cavities can produce pleural effusions and the development of respiratory symptoms. Patients may become aware of an abdominal or nodal mass either in the inguinal region, axillae or the supraclavicular fossa.

Following a full clinical assessment, measurement of serum CA 125 is routinely used to aid diagnosis. However, its utility to detect early disease is questionable as it is elevated only in about 50% of patients with the International Federation of Gynecology and Obstetrics (FIGO) stage I disease. In advanced disease, CA 125 is elevated in about 85% of patients. It is not specific for ovarian cancer and raised CA 125 levels may be found in non-gynaecological malignancies (e.g. breast, lung, colon and pancreatic cancer) and benign disease (e.g. endometriosis, pelvic inflammatory disease and ovarian cysts). Serum carcinoembryonic antigen (CEA) and CA 19–9 levels are sometimes measured in situations where it is unclear whether an ovarian mass is of gastrointestinal origin, or a primary mucinous ovarian tumour. Similarly, in these situations, colonoscopy and/or gastroscopy are sometimes considered, particularly when CA 125/CEA ratio is ≤25. Ultrasonography of the abdomen and pelvis is usually the first imaging investigation recommended for women in whom ovarian cancer is suspected. Transvaginal ultrasonography has improved the visualisation of ovarian structures, thus improving the differentiation of malignant versus benign conditions [17]. A number of morphological variables have been identified as being strongly associated with ovarian cancer. The presence of a large lesion, multi-locular cysts, solid papillary projections, irregular internal septations and ascites are highly suggestive of ovarian cancer. A 'risk of malignancy' index can be calculated from clinical factors, ultrasound and CA 125 and can be used to refer patients to a specialist gynaecological oncology team. Computed tomography (CT) scans are routinely used to determine the extent of disease and to aid in surgical planning. Imaging of the chest with CT or chest X-ray should be done to look for pleural effusions and disease above the diaphragm. A pleural effusion cannot be regarded as malignant and indicative of FIGO stage IV disease without confirmation of positive cytology. Magnetic resonance imaging (MRI) scans do not form part of routine investigations.

staging and risk assessment

FIGO staging remains the most powerful indicator of prognosis (see Table 1). Although surgically defined, preoperative assessment with cross-sectional imaging (CT or MRI) is essential as it guides surgery and the pathway of intervention. Given the variation in histological subtypes and evolving different patterns of care, reliance on a cytological diagnosis should be avoided and a histological diagnosis should be obtained if at all possible. Primary surgery remains the most common and preferred approach, but where this is deemed not feasible, an image-guided or laparoscopic biopsy should be carried out.

treatment plan

surgical management of early primary disease

The aim of surgery for early ovarian cancer is to resect the tumour and to undertake adequate staging. This will provide prognostic information and will define whether chemotherapy is needed. The diagnosis may be made preoperatively, but sometimes a tumour is an incidental finding. The availability of

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 histologically 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.

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a frozen section to identify a malignant epithelial cancer may allow the necessary surgical staging to be done, without the need for a second operative procedure. Accurate surgical staging is important as it may unmask occult advanced disease. Depending on the histological grade and subtype, ≤30% of the patients with apparently early epithelial ovarian cancer will be upstaged after comprehensive surgical staging [18, 19]. Cass et al. showed that, in 96 patients with grade 3 tumours and gross disease confined to one ovary, 15% had microscopically positive lymph nodes [20]. Among these patients, 50% had positive pelvic nodes, 36% had positive para-aortic node and both were positive in 14% of the cases. Maggioni et al. reported on a prospective randomised trial of systematic lymphadenectomy in patients with ovarian cancer macroscopically confined to the pelvis. Positive nodes were detected in 22% of patients undergoing systematic lymphadenectomy, compared with only 9% of patients who underwent merely a sampling ($P = 0.007$). Although a trend for improved progression-free survival (PFS) and overall survival (OS) was observed for the lymphadenectomy group when compared with the control group, the study lacked the statistical power to be conclusive in this respect [21]. Thus, there is currently no evidence to suggest that lymphadenectomy *per se* improves survival. Bulky lymph nodes should be resected in an effort to remove all visible residual disease. Adequate, non-fertility-sparing surgery should consist of peritoneal washings, ideally taken before manipulation of the tumour, bilateral salpingo-oophorectomy, hysterectomy, multiple peritoneal biopsies of all abdominal fields, at least infracolic omentectomy, appendectomy in case of mucinous histology and pelvic and para-aortic lymph node dissection up to the renal veins.

When young women are affected, fertility-sparing surgery could be considered in early-stage disease, but always after thoroughly informing the patient about the potential risks. Patients with stage IA or stage IC with unilateral ovarian involvement and favourable histology, that is mucinous, serous, endometrioid or mixed histology and grade 1 or 2, would be amenable to organ-preserving surgery, but only in combination with complete surgical staging. This would include a lymphadenectomy to exclude more advanced disease. In large retrospective analyses, women with G3 disease or stage IC with clear-cell histology had a higher risk of recurrence. However, this increased risk is mainly related to a higher incidence of extraovarian spread observed in grade 3 tumours, rather than to a higher relapse rate in the preserved ovary [22]. Therefore, these patients should be carefully informed about their prognosis to enable them to make a personalised and thorough choice.

surgical management of primary advanced ovarian cancer

In advanced epithelial ovarian cancer, the aim is complete cytoreduction of all macroscopic visible disease, since this has been shown to be associated with a significantly increased OS and PFS [23–25]. In order to achieve this, a maximal surgical effort is required, including intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky para-aortic lymph nodes and splenectomy. There is an increasing body of evidence that suggests specialist training and surgical expertise results in improvements in the rate of cytoreduction, with no increase in morbidity as a result of this process [26]. Thus, women with advanced disease are advised to undergo surgery in specialised centres with adequate infrastructure and training [B]. Optimal cytoreduction is defined as total macroscopic tumour clearance with no residual visible disease. A recent meta-analysis evaluating the surgical outcome of more than 3120 patients showed that residual tumour is a more powerful prognostic determinant than FIGO stage; patients with suboptimally debulked stage IIB–IIIB tumours had a worse outcome that those with completely debulked stage IIIC tumours [23]. The value of systematic pelvic and para-aortic lymphadenectomy in advanced disease remains controversial. A retrospective analysis of more than 1900 patients found that lymphadenectomy was associated with a prolonged survival in patients with no gross residual disease [27]. However, a prospective randomised trial of lymphadenectomy versus removal of bulky nodes in patients with <2 cm residual tumour showed an improvement in PFS but not OS for the lymphadenectomy group [28]. A large multi-centre, prospectively randomised trial of lymphadenectomy in this group of patients just completed accrual (LION Trial, AGO-OVAR OP.3 [NCT00712218]). Until the results of such trials become available, systematic lymphadenectomy should not be regarded as a standard procedure. Currently, the removal of bulky lymph nodes is carried out as part of an attempt to achieve maximum cytoreduction.

The timing of surgical cytoreduction in relation to chemotherapy is still debated. A large prospective trial showed [25] that in advanced bulky stage IIIC or IV disease, three cycles of platinum-based neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy [I, A]. Surgical morbidity had a non-significant trend to be lower in the neoadjuvant arm. As a result of these data, the use of primary chemotherapy with interval surgery is becoming more widely accepted and is offered to patients with poor performance status at presentation, low albumin levels and in those with very extensive tumour dissemination. Validation of the results of this approach may come from further trials that are ongoing. The place of secondary interval debulking surgery after primary surgery with suboptimal cytoreduction and three cycles of chemotherapy is less clear. Improved survival following secondary surgery was seen in the European Organisation for Research and Treatment of Cancer (EORTC) trial [24], but it was not confirmed by another trial conducted by the Gynaecological Oncology Group (GOG) [29]. However, differences in the extent of primary cytoreduction and the use of paclitaxel with platinum may account for the discordant results.

A 'second look' diagnostic laparoscopy or laparotomy after completion of treatment to assess intraperitoneal status is obsolete and should not be carried out, as its impact on survival has never been demonstrated.

surgical management of relapsed ovarian cancer and surgery for palliation

The value of surgical cytoreduction in relapsed epithelial ovarian cancer remains controversial and is not regarded as a standard of care, as the evidence for this approach has not been demonstrated in prospective trials. In retrospective analyses,

surgery at first relapse appears to be associated with a survival benefit only when a complete tumour resection can be obtained [30, 31]. Patients with two of three of the following criteria: complete resection at first surgery, good performance status and absence of ascites had the best survival [III, C]. There are currently two prospective multi-centre randomised trials evaluating the value of surgery at relapse. The European trial, DESKTOP III [NCT01166737] uses selection criteria based on the above. The other study GOG 213 [NCT00565851] also incorporates the addition of bevacizumab to chemotherapy.

The value of surgery to improve palliation at later relapse is less clear. The largest multi-centre retrospective analysis on tertiary cytoreduction included more than 400 patients in 14 centres worldwide [32]. This analysis showed that residual tumours retain a positive effect on survival even in the tertiary setting of epithelial ovarian cancer, attenuating the impact of other well-established negative prognostic predictors of survival such as ascites, advanced FIGO stage and peritoneal carcinomatosis [IV, C].

adjuvant chemotherapy for early-stage disease

A recent Cochrane meta-analyses of five 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 [33]. 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. Long-term follow-up of the ICON 1 trial confirms the benefit of adjuvant chemotherapy, particularly in those patients at higher risk of recurrence (stage 1B/C grade 2/3, any grade 3 or clear-cell histology) [34]. Therefore, adjuvant chemotherapy should be offered not only to suboptimally staged patients but also to those optimally staged at higher risk of recurrence [I, A].

The optimal duration of treatment remains controversial; there has been only one randomised trial (GOG 157) which showed that six cycles of carboplatin and paclitaxel were not associated with longer PFS or OS, but with a significantly greater toxicity than with three cycles [35]. There are no data to demonstrate that the addition of paclitaxel to carboplatin is superior. Some clinicians feel that separating the choice of treatment between FIGO stage IC and stage II–IV is artificial, and therefore choose to offer combination chemotherapy to women with stage IC. However, evidence of a benefit of combination therapy in this group is lacking; therefore, it is reasonable to consider single-agent carboplatin to all women with intermediate and high-risk stage I disease.

front-line chemotherapy for epithelial ovarian cancer (FIGO stage II–IV)

The risks of recurrence for disease spread beyond the ovary are significant, and chemotherapy is recommended for all patients with FIGO stage II–IV disease post surgery.

Standard chemotherapy consists of a combination of paclitaxel 175 mg/m^2 and carboplatin AUC 6-5, both administered intravenously every 3 weeks [I, A] [36–38]. This has been the standard treatment of more than 15 years, and clinical trials in the last decade adding a third drug, such as the large Gynaecologic Cancer InterGroup (GCIG) ICON-5/GOG 182 trial [39], have not been shown to improve PFS or OS in these patients. The combination of cisplatin and paclitaxel is equally effective but is more toxic and less convenient to administer. Usually six cycles of treatment are given; no evidence exists to suggest that more than six cycles results in a better outcome. While survival benefits are seen in trials with platinum-based therapy, many women undergo several lines of treatment, making dissection of the contribution of individual therapies, particularly first-line therapy, more complex.

For those patients who develop an allergy to or do not tolerate paclitaxel, the combination of docetaxel-carboplatin or pegylated liposomal doxorubicin (PLD)-carboplatin can be considered an alternative, based on two randomised clinical trials that showed similar efficacy [II, A] [40, 41].

Alternative schedules of administration of paclitaxel and platinum chemotherapy have included intraperitoneal delivery and dose-dense regimens.

Intraperitoneal chemotherapy has a solid pharmacokinetic background and consists of administration of part of the chemotherapy, usually the platinum agent, directly into the peritoneal cavity through a catheter. One randomised clinical trial carried out by the GOG (GOG-172) demonstrated a benefit in PFS and OS for a regimen that included not only intraperitoneal cisplatin on day 2 and intravenous paclitaxel on day 1, but also intraperitoneal paclitaxel on day 8 [42]. Additionally a meta-analysis of five clinical trials confirmed a benefit for intraperitoneal chemotherapy in OS [43]. This led to a National Cancer Institute alert in 1996 recommending that intraperitoneal therapy should be considered in patients with small volume (<1 cm) or no residual disease after surgery. However, this treatment has not been adopted as a standard of care in the majority of institutions and countries due to its greater toxicity and difficulty in delivering all of the planned treatment. The absence of the current standard intravenous control arm in these trials has further influenced scepticism, and many clinicians still regard intraperitoneal therapy as experimental, recommending its use only in the context of randomised trials. Several of these are in progress [I, B].

Dose-dense scheduling to improve the effectiveness of paclitaxel chemotherapy has also been explored in ovarian cancer. A Japanese study (NOVEL–JGOG 3062) compared 3-weekly paclitaxel and carboplatin with the same dose of carboplatin every 3 weeks (AUC 6) and paclitaxel administered in a weekly dose of 80 mg/m^2. Significant benefits in PFS and OS were seen at 3 years, and a recent update with longer follow-up has confirmed this benefit in women with small volume and >2 cm residual disease [44, 45]. However, 36% of patients had to stop this regimen prematurely due to side-effects, especially myelotoxicity. This is a potentially practice-changing trial, but the possibility that this is a chance finding or is due to a pharmacogenomic difference between Japanese and Caucasian populations makes it necessary to confirm these results in a

Caucasian population. Two trials are in progress (GOG 262 [NCT01167712] and ICON 8 [NCT01654146]) and one was recently completed (MITO 7 [NCT00660842]), but in the absence of confirmatory data, dose-dense administration of paclitaxel currently can only be considered an option, and not as a standard of care [I, B].

targeted therapy

Angiogenesis is an important component driving the growth of ovarian cancer. Two large randomised clinical trials (GOG-218 and ICON-7) have assessed the addition of bevacizumab to the combination of paclitaxel and carboplatin in front-line therapy [46, 47]. Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor. In both trials patients in the experimental arm received bevacizumab intravenously every 3 weeks during the chemotherapy phase, followed by a limited period of maintenance with the same schedule of bevacizumab. GOG-218 included a second experimental arm of bevacizumab with chemotherapy, followed by maintenance with a placebo. There were significant differences in both trials in terms of dose (7.5 mg/kg in the ICON-7 versus 15 mg/kg in the GOG-218), duration (12 months in the ICON-7 versus 15 months in the GOG-218) and patient characteristics (GOG-218 included only patients with stage III–IV and macroscopic residual disease after surgery, but ICON-7 included patients also with high-risk early stage, and patients in a more advanced stage but without macroscopic residual disease after surgery). Both trials met their primary end point, which was PFS for the two bevacizumab maintenance arms. The test for interaction in the ICON-7 trial showed that a greater benefit was observed in the 'high-risk' population, defined as those patients with stage III–IV and residual disease >1 cm. In an interim analysis, OS was prolonged in this group. No survival difference was observed in GOG-218 and mature survival results from ICON-7 are awaited. Bevacizumab has been licensed by the European Medicines Agency (EMA) at 15 mg/kg, with carboplatin and paclitaxel and for ≤15 months or until progression. Bevacizumab is not licensed for ovarian cancer in the USA, and it is not consistently used in Europe. Some clinicians restrict the use of the drug to the subgroup of 'higher risk' patients as defined in the ICON-7 trial, and some are awaiting the mature survival data from ICON 7, while others use the drug in its licensed dose and indication or use the drug in patients with recurrent ovarian cancer. The addition of bevacizumab is recommended for patients with advanced ovarian cancer with poor prognostic features such as stage IV or suboptimal debulking as defined in the ICON-7 trial [I, B]. Bevacizumab should be given with paclitaxel or carboplatin with a treatment duration of one year. Trials with other anti-angiogenic drugs and extended therapy with bevacizumab are ongoing.

evaluating the response to treatment

As CA 125 is elevated in most patients with advanced disease, serial measurement is a useful marker to assess the response to chemotherapy according to GCIG criteria [48]. Where there is visible disease on CT at the beginning of chemotherapy, some clinicians will formally evaluate a response on CT halfway through chemotherapy. A CT should be carried out before interval debulking surgery or at the end of first-line chemotherapy, to confirm the disease status. If the CA 125 does not reach the normal range before the end of chemotherapy, or if there is residual disease on CT, the disease status would be regarded as a 'partial response' to front-line treatment.

chemotherapy in recurrent ovarian cancer

Despite optimal upfront surgery and the administration of front-line paclitaxel–carboplatin chemotherapy, ~70% of patients will relapse in the first 3 years.

The prognosis and probability of response to second-line therapy and subsequent lines depends in great part on the progression-free interval after the last dose of the preceding line of chemotherapy. These categories are based on the response to a rechallenge with platinum-based drugs but probably apply to non-platinum therapies as well. A categorisation, recently updated and confirmed by the GCIG 4th Ovarian Cancer Consensus Meeting, defines 'platinum-refractory' as patients progressing during therapy or within 4 weeks after the last dose; 'platinum-resistant' patients progressing within 6 months of platinum-based therapy; 'partially platinum-sensitive, patients progressing between 6 and 12 months; and 'platinum-sensitive' patients progressing with an interval of more than 12 months (GCIG Consensus) [49]. It should be noted that these categories are based on observational studies and that the categorisation is probabilistic, with the likelihood of response being a continuous variable. Furthermore, the category of 'platinum-resistant/refractory' comprises patients whose disease recurs after one or several lines of treatment. The biological behaviour of the tumour in these groups may be very variable, with differing growth rates and distribution of symptoms requiring different approaches to treatment.

Treatment of patients with 'platinum-resistant or refractory' disease should be focused on quality of life and control of symptoms. Traditionally, this is a poor prognosis population with a short expected OS, usually <12 months. Four different agents, weekly or 3-weekly paclitaxel, topotecan, PLD and gemcitabine, have been shown to have some activity in phase III trials, with overall response rates no >15% and a median PFS of 3–4 months. Occasionally, platinum drugs continue to be used in the 'platinum-resistant' population with, for example, a dose-dense regimen. However, as no agent has proven to be superior to another, the selection of therapy should be based on toxicity, clinical situation of the patient and convenience of administration. Randomised trials of combination chemotherapy have shown no advantage in this population; it compounds toxicity. Accordingly, sequential single-agent therapy is the recommended management for this group of patients [I, A].

For those patients with a later relapse, over 6 months and especially over 12 months, carboplatin-doublet should be the treatment of choice [I, A]. Trials have included carboplatin compared with the same drug combined with paclitaxel, gemcitabine or an anthracycline. All have shown an improvement in PFS but a survival benefit was only seen with the carboplatin–paclitaxel combination (ICON 4/OVAR 2.2) [50]. A meta-analysis including four randomised trials

confirmed an improvement in PFS with a HR of 0.68 (95% CI 0.57–0.81) and OS with a HR of 0.8 (95% CI 0.64–1.0) [51]. Additionally, the CALYPSO trial demonstrated that the combination of carboplatin–PLD was not inferior to paclitaxel–carboplatin in terms of PFS, but was better tolerated because of the minimal incidence of alopecia, neuropathy, and arthralgias and fewer hypersensitivity reactions [52]. Again, the selection between the different options of platinum-based doublets should be based on the toxicity profile and convenience of administration [I, B].

Several choices of treatment exist for patients with 'platinum-sensitive' relapse. As this can occur on more than one occasion, it allows for different combinations to be selected. Most of these combinations involve platinum, but in the 'partially platinum-sensitive' group, a survival benefit was seen in a subgroup analysis of the OVA-301 trial when trabectedin was combined with PLD, when compared with PLD alone [I, B] [53, 54]. It has been hypothesised that this benefit is due to the restoration of 'platinum-sensitivity' by artificially prolonging the platinum-free interval. This is now being explored in two prospective randomised trials.

targeted therapy

Bevacizumab has shown to improve the PFS of recurrent ovarian cancer in two randomised phase III trials. The first (OCEANS trial) included patients with measurable recurrent ovarian cancer after first-line and a platinum-free interval longer than 6 months. All patients received a combination of carboplatin and gemcitabine at standard doses and were randomised to receive bevacizumab (15 mg/kg) or placebo administered every 3 weeks until progression. The addition of bevacizumab to chemotherapy increased significantly the PFS (HR 0.48, 95% CI 0.38–0.60) and produced an increment in the response rate of 21% (ORR 78.5% versus 57.4%, $P < 0.0001$)] [55]. A more mature survival analysis has not proven any additional benefit in OS, probably due to the high rate of crossover (41% of patients in the control arm received bevacizumab at some point during progression) [I, A]. However, bevacizumab in combination with this chemotherapy has been licensed by the EMA and is a recommended treatment for patients with 'platinum-sensitive' relapsed ovarian cancer who have not previously received bevacizumab.

The second (AURELIA) trial was carried out in patients with 'platinum-resistant' ovarian cancer. This was a selected group who had received no more than two previous lines of treatment and who did not have evidence of bowel obstruction or tumour involvement of the serosa of the rectosigmoid colon. Patients received standard chemotherapy according to physician choice (weekly paclitaxel, PLD or topotecan), and were randomised to receive bevacizumab or no additional treatment, together with chemotherapy and then as maintenance until progression. Patients receiving bevacizumab had a longer PFS (HR 0.48, 95% CI 0.38–0.60) and an increment in response rate measured by Response Evaluation Criteria in Solid Tumors (RECIST) of 15% (11.8% versus 27.3%) [I, B] [56]. However, quality of life and OS data are still pending.

follow-up

Relapse may be defined according to CA 125 criteria even if this does not directly lead to a change in treatment. More often, a rising CA 125 triggers further imaging. According to GCIG criteria, progression or recurrence based on serum CA 125 levels is defined on the basis of a progressive serial elevation of serum CA 125 [48]. Elevated values must be confirmed by two separate measurements obtained at least one week apart. CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted.

The value and type of follow-up after primary therapy has a weak evidence base and as a result practice varies. Clinical evaluation with or without pelvic examination and measurement of CA 125 is often carried out every 3 months for 2 years, then every 6 months during years 4 and 5 or until progression occurs. While the benefit of monitoring CA 125 during therapy is clear, the value of its measurement following

Table 2. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

the completion of treatment is less certain. A phase III randomised study (OV05-EORTC 55955) comparing the early intervention of second-line therapy based on elevated CA 125 compared with treatment begun on clinical evidence of relapse showed no OS advantage of early CA 125-directed retreatment. Treatment was delayed by a median of 4.8 months with no detriment to OS (HR 1.01; 95% CI 0.82–1.25; $P = 0.91$) [57] [I, A]. Similarly, third-line treatment was begun 4.6 months earlier in the patients who had regular CA 125 monitoring. Quality of life was lower in the early treatment group, presumably because this group was exposed to more chemotherapy. While some clinicians no longer measure CA 125 as part of follow-up, others do as there is a possibility of missing surgically resectable recurrence if CA 125 is not measured. The results of ongoing trials will determine whether surgery for relapse improves survival. Practice depends on local follow-up and patients wishes; some patients prefer to have the reassurance of a normal CA 125 reading. Many clinicians have interpreted the results of OV05-EORTC55955 as showing that it is safe to delay the reintroduction of chemotherapy up to the appearance of symptoms when the CA 125 is rising, provided the patient is well, the disease volume on CT scan is small and there is no evidence of compromised organ function.

PET-CT scans may reveal sites of disease not visible on CT scans. The principal role of this imaging modality is to help the selection of patients for secondary debulking surgery, by excluding additional sites of disease not seen on CT scans and not amenable to cytoreduction.

personalised medicine

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 2. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

Prof. Ledermann has reported research funding support from AstraZeneca, consultancy and/or speaker's bureau with no personal renumeration from AstraZeneca, MSD/Endocyte, Clovis, Glycotype and Roche and Boehringer Ingelheim; travel grants from Roche and Boehringer Ingleheim. Dr Raja is supported by grant funding from Cancer Research UK (C444/A15953). Dr Gonzalez-Martin has reported speaker's bureau for Roche, PharmaMar. Dr Colombo has reported consultancy/honoraria from GlaxoSmithKline, Merck Serono, Roche, Amgen, PharmaMar, Clovis. Dr Fotopoulous and Prof. Sessa have declared no potential conflicts of interest.

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