Ovarian cancer

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Gynaecological cancer accounts for approximately 5% of all new cancer cases in the UK and is a significant cause of morbidity and mortality. The majority of gynaecological cancers occur in patients older than 60 years of age and some such as uterine cancer present early with postmenopausal bleeding and as such can be diagnosed and treated at an early stage with 5-year survival rates approaching 90%. However, ovarian cancer commonly presents at an advanced stage with non-specific symptoms and as a result carries a very poor prognosis. Therefore, ovarian cancer represents a major therapeutic challenge and mortality rates from this aggressive disease have remained high with little improvement over the past 30 years.

Pathology

The ovaries are a common site of cancer and include tumours arising from germ cells, sex-cord stromal cells and other rare cell types as well as secondary metastatic disease from sites such as endometrium, breast, colon and stomach. However, the majority of ovarian cancers (greater than 70%) are epithelial in origin and are derived from a single layer of cuboidal epithelium surrounding the ovary. Epithelial ovarian cancer (EOC) is thought to arise because of recurrent insults to this layer due to ovulation. EOC is a heterogenous disease that can be classified according to cell type into serous, mucinous, endometroid, clear cell and Brenner (transitional) tumours. The majority of EOC cases are serous carcinomas that can be further subdivided into two distinct subtypes. High grade serous carcinomas (75%) are more aggressive, metastasise rapidly and are associated with a poor prognosis whereas low-grade serous carcinomas (25%) appear to follow a more indolent course.[1] In addition to invasive EOC, benign and borderline malignant tumours also arise from ovarian epithelial cells and these tumours are thought to be precursor lesions of many of the different types of EOC.

Epidemiology

The lifetime risk for the development of ovarian cancer is one in 48 (2·1%) and according to recent statistics EOC is now the most commonly diagnosed form of gynaecological cancer in women. It is also the most common cause of mortality and accounts for more deaths than all other gynaecological cancer types put together. In 2004, there were 6,700 new cases of ovarian cancer in the UK (2% of total new cancer cases) and 4,700 deaths.[2] Ovarian cancer is primarily a disease of postmenopausal women with 85% of cases diagnosed in women older than 50 years and the highest incidence rates found in patients older than 65 years. Recent evidence indicates that nulliparity, early menarche and late menopause are all associated with an increased risk of ovarian cancer whereas pregnancy and use of the oral contraceptive pill reduce the risk.[3] Hereditary EOC accounts for only about 5–10% of ovarian cancer cases. The vast majority of these cases are related to germline mutations in BRCA1 and BRCA2. The presence of a germline mutation in BRCA1 or BRCA2 confers a 16–44% and a 10% lifetime risk of developing EOC respectively in comparison to a 2·1% lifetime risk in the general population.[4,5] A small number of hereditary EOC cases are due to mutations in genes involved in mismatch repair (MSH2 and MLH1). This type of ovarian cancer is associated with hereditary non-polyposis colon cancer (HNPCC) and is also known as Lynch syndrome II.[6] These patients are also predisposed to colon and endometrial cancers.

Box 1: Staging system for epithelial ovarian cancer. Guidelines from Federation of Gynaecology and Obstetrics

Stage		Charateristics
I		Tumour limited to ovaries
	A	One ovary involved without ascites, positive peritoneal washings, surface involvement or rupture.
	B	Both ovaries involved without ascites, positive peritoneal washings, surface involvement or rupture.
	C	Ascites, positive peritoneal washings, surface involvement or rupture present.
II		Ovarian tumour with pelvic extension.
	A	Involvement of the uterus or fallopian tubes.
	B	Involvement of other pelvic organs (eg. bladder, rectum or pelvic side wall).
	C	Pelvic extension plus ascites, positive peritoneal washings, surface involvement or rupture present.
III		Tumour involving the upper abdomen or lymph nodes.
	A	Microscopic disease outside the pelvis, typically involving the omentum.
	B	Gross deposits ≤2cm in diameter.
	C	Gross deposits ≥2cm or nodal involvement.
IV		Distant metastatic disease.

Clinical features

Other gynaecological cancers such as cervical and uterine cancer tend to present early with abnormal vaginal bleeding. In contrast, early-stage ovarian cancer is commonly asymptomatic and patients tend to present at more advanced stages with symptoms including abdominal distension and bloating, nausea, anorexia, constipation and abnormal vaginal bleeding.[7] Pelvic pressure symptoms such as urinary frequency can be related to a large ovarian mass. The ovaries are generally impalpable in postmenopausal women and the clinical finding of an ovarian mass should arouse a high degree of suspicion.

Investigation

Women with suspected ovarian cancer should be investigated promptly with full blood count, clinical biochemistry, liver function tests, serum Ca125 and transvaginal ultrasound. A risk of malignancy index (RMI) can be calculated based on menopausal status, the findings of transvaginal ultrasound and the Ca125 level (normal= <35U/ml).[8] An RMI score greater than 200 indicates a strong likelihood of malignancy. Women diagnosed with probable ovarian cancer should have a chest x-ray, with sampling of any pleural effusions, and also undergo a CT scan of chest, abdomen and pelvis prior to any planned surgical procedure.

Treatment

Surgery

Surgery is the mainstay of treatment in ovarian cancer and although definitive therapy is the primary aim, accurate surgical staging is necessary in order to aid further treatment decisions. Surgical staging involves the systematic exploration of the entire abdomen through a midline incision. All intra-abdominal surfaces should be examined and any ascites aspirated, if no ascites is present then peritoneal washings should be taken. Comprehensive surgery in ovarian cancer consists of hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymph node sampling, biopsy of any suspicious lesions.[9] If possible an ovarian tumour should be removed intact. Bowel resections are necessary in up to 30% of patients. Staging is based on the FIGO system and described in box 1. The main aim of surgery in ovarian cancer is optimal cytoreduction with resection of tumour leaving no residual deposits greater than 1cm in size. Prognosis is related to success of cytoreduction and a large meta-analysis has demonstrated that patients have improved overall survival following optimal surgery compared to those where only sub-

optimal surgery was possible (40 months versus 16 months). Primary cytoreductive surgery can even be beneficial in patients with stage IV disease. If primary surgery is not possible then secondary cytoreduction can be performed after a course of neo-adjuvant chemotherapy.

Chemotherapy

Following surgery most patients with EOC are considered for post-operative treatment with chemotherapy. A number of prognostic factors are available to guide physicians when considering patient prognosis and the likelihood of treatment success or failure. These include tumour stage, age, optimal cytoreduction, tumour grade, tumour cell type and Ca-125 level.[10,11] A small number of patients with stage IA, grade I disease have a 90–95% 5 year survival, which is not significantly improved with adjuvant treatment, therefore, these patients do not require post-operative chemotherapy.[10] Histological subtype and grade are valuable prognostic features and can be used to assign treatment in EOC. Patients with stage IA disease, but who have grade III, clear cell carcinoma, have a 30–40% chance of relapse, therefore, these patients should be offered adjuvant chemotherapy.[10] Other patients with stage Ic to IIa EOC do derive benefit from adjuvant chemotherapy with a 8% improvement in 5-year survival.[12] Pre-operative elevation of Ca-125 is related to volume of disease and occurs in 85% of patients. Elevation of post-operative Ca-125 has been shown to be an independent prognostic factor.[10] In addition, Ca-125 levels can be monitored following treatment and can be used as a predictive marker of relapse.

Advanced stage EOC is, in the initial stages at least, a very chemosensitive disease and early chemotherapy treatment utilised single agent alkylating agents such as cyclophosphamide, melphalan and thiotepa. These agents were associated with overall response rates of 30–65% including a complete response in 20% and median survivals of up to 17 months.[13] The discovery in the 1960s that platinum exhibited anti-tumoural activity lead to early clinical trials, which suggested that cisplatin demonstrated activity in patients with EOC refractory to alkylating agents. Subsequently, a randomised clinical trial demonstrated that combining cisplatin and cyclophosphamide resulted in significantly improved disease free and overall survival. The improvements reported with platinum based treatment were subsequently confirmed in other randomised trials.[13] Since these early studies, platinum agents have become the single most important drug in the treatment of EOC and indeed a large meta-analysis of 37 trials involving 5,000 patients confirmed the superiority of platinum containing regimens over non-platinum regimens.[14]

The taxane group of chemotherapy agents are derived from the bark of the Pacific Yew tree and paclitaxel has been isolated as the active constituent. Studies of the activity of paclitaxel as single agent therapy in patients with advanced EOC, which is refractory to other chemotherapy drugs, demonstrated that up to 25-30% of patients responded to this agent.[15] This prompted the design of randomised phase III trials examining the substitution of paclitaxel over cyclophosphamide in what was the current standard of care (cisplatin + cyclophosphamide). These studies (which included sub-optimally debulked stage II, III and IV patients) demonstrated that both response rates (58–73% versus 45–50%) and complete response rates (CR 40–50% versus 27–30%) were higher in those patients who received the taxane regimen compared to the non-taxane containing regimen.[16,17] In addition to improved response rates, there was a significantly improved disease free (18 versus 13 months) and overall survival (38 versus 26 months) in favour of the taxane arms of these studies. Finally, further studies have reported that the combination of paclitaxel and carboplatin is equivalent in efficacy to paclitaxel and cisplatin with significantly less renal and neurological toxicity.[18] In summary, paclitaxel chemotherapy in combination with a platinum agent results in response rates of up to 70% and median survival of 3–4 years in patients with advanced ovarian carcinoma.

Treatment of recurrent disease

Although response rates to first-line chemotherapy are high and 50% of patients will have complete remission (as observed by CT scanning and by analysis of Ca-125 levels), the majority of patients with EOC will relapse and only 10–30% will have long-term survival.[9] The treatment options for relapsed ovarian cancer are dependent on the duration of disease free period following platinum based first-line chemotherapy. Further surgery may be considered for patients who relapse after a long disease free interval (>12 months)

if there is the possibility of complete resection. In addition, tumours recurring after 12 months would still be considered platinum sensitive and it is reasonable to retreat these patients with single agent carboplatin with expected response rates of up to 30%. Furthermore, a recent study using retreatment with paclitaxel/carboplatin also demonstrated a high response rate and prolonged survival.[19]

Following first line platinum based chemotherapy, patients who achieve a remission of less than 12 months but greater than 6 months have partially platinum sensitive disease whereas those who only achieve a short remission of less than 6 months are said to be platinum resistant. Those who do not respond to initial platinum chemotherapy have refractory disease.[20] In these situations second-line therapy can be considered and could involve single agent treatment using one of a number of different agents including paclitaxel (given on a weekly schedule), etoposide, topotecan, gemcitabine or liposomal doxorubicin. A review by NICE, evaluating second-line treatment of ovarian cancer, recommended liposomal doxorubicin as treatment for platinum resistant/refractory ovarian cancer.[21] This recommendation was based on a number of trials, which demonstrated no difference in efficacy between paclitaxel, topotecan and liposomal doxorubicin. However, liposomal doxorubicin was more cost effective. This drug is associated with a response rate of 20%, disease free survival of up to 16 weeks and median survival of up to 63 weeks.

Prognosis

The overall 5 year survival for all patients with ovarian cancer is 46%.[2] Older patients generally have a poorer outcome with a 25% 5-year survival for patients aged 60–69 years. The most informative prognostic factor is tumour stage. In the few patients who present with stage IA/Grade I disease, 5-year survival rates can be as high as 95% whereas in patients who present with stage III or IV disease 5-year survival is only 10–30 %.[10]

Conclusion

The treatment of EOC continues to represent a major clinical challenge and the majority of cases will eventually become resistant to currently available chemotherapy agents. Major research into development of new cytotoxic and molecularly targeted drugs is ongoing and is providing early promise. In addition, identification of molecular biomarkers and gene expression signatures will advance efforts to individualise treatment in order to maximise benefit and minimise toxicity from chemotherapy.

Conflict of interest: none declared

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