First-line chemotherapy for the treatment of women with epithelial ovarian cancer

Recommendations for the use of first-line chemotherapy for the treatment of women with epithelial ovarian cancer

June 2014 | Incorporates published evidence to March 2014

A CLINICAL PRACTICE GUIDELINE DEVELOPED BY CANCER AUSTRALIA

This document supplements information about use of chemotherapy for women with epithelial ovarian cancer (Chapter 11) contained in the Clinical practice guidelines for the management of women with epithelial ovarian cancer, 2004.[1]

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Purpose

This guideline includes statements and recommendations based on available, high-level evidence about the use of first-line chemotherapy for the treatment of women with epithelial ovarian cancer. The guideline provides health professionals with information designed to assist in making management recommendations for improved patient outcomes. Cancer Australia also develops information specifically for consumers about ovarian cancer and treatment options.

Endorsed by:

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Background

In 2010, ovarian cancer was the second most commonly diagnosed gynaecological cancer in Australia, with a total of 1,305 ovarian cancer cases diagnosed.[2] It is the most common cause of gynaecological cancer death, representing over half (56%) of such deaths.[3] The five-year relative survival rate for Australian women with ovarian cancer has increased significantly, from 32.4% in 1982-1987 to 43.3% in 2006-2010.[4]

Most women diagnosed with epithelial ovarian cancer are treated with surgery and chemotherapy with the aim of eliminating detectable disease. Primary cytoreduction aims to remove as much of the tumour as possible, to allow adjuvant treatment to be more effective. The Gynecologic Oncology Group (GOG) defines optimal cytoreduction as having residual tumour nodules each measuring 1 cm or less in maximal diameter, with complete cytoreduction (microscopic disease) being the ideal surgical outcome.[5] Ovarian cancer is surgically staged, based on the extent of the disease, using the guidelines established by FIGO (International Federation of Gynecology and Obstetrics).[6] All women with a suspected or diagnosed gynaecological cancer should have access to a comprehensive multi-disciplinary team led by a gynaecological oncologist to provide high quality management tailored to their needs to achieve the best outcome for each woman.[7] Epithelial ovarian cancer (EOC) is a highly chemosensitive tumour, but most women with advanced EOC initially responding to first-line chemotherapy will eventually relapse.[8]

This guideline represents an update of the 2004 guidelines Clinical practice guidelines for the management of women with epithelial ovarian cancer for first-line chemotherapy for treatment of women with epithelial ovarian cancer.[1]

A systematic review on first-line chemotherapy for women with epithelial ovarian cancer was undertaken to identify areas requiring revision in relation to the 2004 guideline recommendations.[9] Details on the literature search including research questions are provided in the Summary of evidence and Summary of study results.

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Recommendations and practice points

The recommendations are based on the statements of evidence for the use of first-line chemotherapy for women with epithelial ovarian cancer. The level of evidence assigned to recommendations is based on the NHMRC Evidence Intervention Hierarchy (Appendix 1). Practice points are also provided to help guide clinical decisions for the use of first-line chemotherapy for women with epithelial ovarian cancer. Practice points are based on expert opinion when the evidence to make a recommendation is insufficient or where the evidence is outside the scope of the systematic review.

Recommendations to individual patients should be based on their circumstances, the absolute benefits and harms of the treatment, other treatments used, quality of life issues and their personal preferences. These factors should be discussed with the woman and her family and carer(s), tailored to her preferences for information and decision-making involvement.

The recommendations for the use of first-line chemotherapy for the treatment of women with epithelial ovarian cancer should be considered within a multidisciplinary team setting.

Multidisciplinary care is the best-practice approach to providing evidence-based cancer care.[10] Multidisciplinary care is an integrated team-based approach to cancer care where medical and allied health care professionals consider all relevant treatment options and collaboratively develop an individual treatment and care plan for each patient.[10]

RECOMMENDATION TUMOURS OF LOW MALIGNANT POTENTIAL	LEVEL OF EVIDENCE[11]	REFERENCE
Adjuvant chemotherapy is not indicated in patients with tumours of low malignant potential (borderline or proliferating), unless invasive peritoneal implants are histologically confirmed.	II	Siedman and Kurman 2000[12]

RECOMMENDATIONS EARLY STAGE OVARIAN CANCER (I-IIA)	LEVEL OF EVIDENCE[11]	REFERENCE
Adjuvant chemotherapy with a platinum compound is recommended for women with high-grade or clear-cell histology as these are known to have a higher recurrence rate.	I	Winter-Roach 2012[13]
Adjuvant chemotherapy is not recommended for patients with comprehensively staged IA or IB well or moderately differentiated tumours, as their risk of relapse is low and the toxicity is not justified.	I	Winter-Roach 2012[13]

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PRACTICE POINT EARLY STAGE OVARIAN CANCER (I-IIA)	REFERENCE
If comprehensive surgical staging has not been undertaken by a certified gynaecological oncologist, the case should be referred for discussion at a multidisciplinary team meeting, for consideration of the option of surgical staging or chemotherapy.	Winter-Roach 2012[13]

RECOMMENDATION ADVANCED OVARIAN CANCER (IIB-IV) - CHEMOTHERAPY	LEVEL OF EVIDENCE[11]	REFERENCE
Standard first-line treatment of advanced epithelial ovarian cancer should contain a platinum compound, either in combination or as a single agent, unless specifically contraindicated.	II	OVAR 11/ ICON7[14] GOG 218[15] OVAR 5[16] OVAR 9[17] GOG 182/ ICON5[18] Bolis 2010[19] OVAR 7[20] OV 16[21] HeCOG[22] Lhomme 2008[23] GOCCNE[24] SGCTG[25] MITO 2[26] SCOTROC[27] GOG 158[28] OVAR 3[29, 30] HeCOG[31] Mouratidou[32] OV 10[33-35] AOCSG[36] Muthuramalingam[37] SCOTROC2A[38] SCOTROC2B[39] Minagawa 2006[40] Mori 2007[41] JGOG3014[42] Fruscio 2008[43]

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RECOMMENDATION ADVANCED OVARIAN CANCER (IIB-IV) -SCHEDULING - NEOADJUVANT CHEMOTHERAPY	LEVEL OF EVIDENCE[11]	REFERENCE
While primary debulking is the usual treatment, neoadjuvant chemotherapy may be considered for selected patients with stage III or IV cancers.	II	Vergote 2010[44]

RECOMMENDATION ADVANCED OVARIAN CANCER (IIB-IV) -SCHEDULING – INTRAPERITONEAL CHEMOTHERAPY	LEVEL OF EVIDENCE[11]	REFERENCE
Women with stage III ovarian cancer who are optimally debulked at primary surgery should be considered for intraperitoneal (IP) chemotherapy. IP chemotherapy should be provided in a centre with appropriate expertise and potential toxicities fully explained.	I	Jaaback 2011[45] Armstrong 2006[46]

PRACTICE POINT ADVANCED OVARIAN CANCER (IIB-IV) – BIOLOGICAL THERAPIES	REFERENCE
Based on data from ICON7, bevacizumab can be considered for first-line treatment of women at high risk (stage IV disease or stage III and >1 cm residual disease), taking into account quality of life issues.	Perren 2011[14]

PRACTICE POINT SCHEDULING- DOSE DENSE CHEMOTHERAPY	REFERENCE
Dose-dense paclitaxel (where time between the administration of chemotherapy drugs is reduced), in combination with 3-weekly carboplatin, can be considered as an option for first-line treatment of advanced epithelial ovarian cancer.	Katsumata, 2009[47] Katsumata 2012[48] Harano 2014[49]

PRACTICE POINT OLDER WOMEN	REFERENCE
Treatment should be considered on an individual basis, and age alone should not be used as a criterion for modifying standard treatment. Adequate geriatric assessment is important to guide appropriate treatment.	Eisenhauer 2007[50]

PRACTICE POINT OBESE PATIENTS	REFERENCE
When treating obese women with epithelial ovarian cancer, clinicians should consider the ASCO guidelines on chemotherapy dosing for obese adult cancer patients. http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.39.9436	Griggs 2012[51]

PRACTICE POINT CLINICAL TRIALS	REFERENCE
Clinical trials have an unquestioned role in improving treatment for future patients and results of several clinical studies have prompted significant changes in practice. It is appropriate for clinicians to discuss participation in clinical trials with women who have ovarian cancer.	Robinson 2009[52] Peppercorn 2004[53]

Statements of evidence

Tumours of low malignant potential

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
Patients with tumours of low malignant potential (borderline or proliferating), even with documented metastases, have an excellent prognosis. In the absence of documented invasive peritoneal implants, adjuvant chemotherapy is not indicated.	II	Siedman and Kurman 2000[12]

Women with early stage ovarian cancer, Stage I-IIA

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
There is evidence from a meta-analysis that indicates that some women with early stage (I-IIA) epithelial ovarian cancer who received adjuvant platinum-based chemotherapy had better 5-year overall survival (HR 0.71; p=0.01) and 5-year progression-free survival (HR 0.67, P=0.0005) than women who did not. Improved overall and progression-free survival for women who received adjuvant platinum-based chemotherapy was maintained at 10 years. OS: HR 0.74, p=0.02. PFS: HR 0.67, p=0.0005	I	Winter-Roach 2012[13]
Sub-group analysis: For women with early stage epithelial ovarian cancer who had comprehensive surgical staging, there was no significant difference in overall survival (two trials) or in progression-free survival (two trials) between those who did and did not receive adjuvant chemotherapy. OS: HR 1.22 (95% CI 0.63 to 2.37), p=0.56. PFS: HR 0.67 (95% CI 0.36 to 1.22), p=0.19. In women who had sub-optimal staging, those who received adjuvant chemotherapy had statistically significantly better overall survival (two trials) and progression-free survival (three trials). OS: HR 0.63 (95% CI 0.46 to 0.85), p= 0.003. PFS: HR 0.64 (95% CI 0.50 to 0.82), p=0.0004	I	Winter-Roach 2012[13]

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
In one trial that reported survival grouped by level of risk, adjuvant chemotherapy improved 10-year overall and progression-free survival in high risk women, but not in those at low/medium risk. OS: HR 0.48 (95% CI 0.32 to 0.72), p=0.00039. PFS: HR 0.52 (95% CI 0.33 to 0.82) p=0.0049		

Advanced ovarian cancer (IIB-IV)- Chemotherapy

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
Almost all regimens which investigated the addition or substitution of a range of agents to the standard regimen of combination carboplatin and paclitaxel, in populations with a majority of advanced stage ovarian cancer patients, failed to demonstrate an overall or progression-free survival advantage.	II	OVAR 11/ ICON7[14] GOG 218[15] OVAR 5[16] OVAR 9[17] GOG 182/ ICON5[18] Bolis 2010[19] OVAR 7[20] OV 16[21] HeCOG[22] Lhomme 2008[23] GOCCNE[24] SGCTG[25] MITO 2[26] SCOTROC[27] GOG 158[28] OVAR 3[29, 30] HeCOG[31] Mouratidou[32] OV 10[33-35] AOCSG[36] Muthuramalingam[37] SCOTROC2A[38] SCOTROC2B[39] Minagawa 2006[40] Mori 2007[41] JGOG3014[42] Fruscio 2008[43]

Advanced ovarian cancer (IIB-IV) – Biological therapies

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
In ICON7, improved progression-free survival was reported in the group receiving bevacizumab compared with standard therapy; HR=0.81 p=0.04. The maximum improvement was at 12 months, co-inciding with the end of planned bevacizumab treatment, and diminished by 24 months.	II	Perren 2011[14]
In ICON7, improved overall survival was reported in a sub-group of patients at high risk of progression when bevacizumab was used in addition to carboplatin and paclitaxel; HR=0.64, p=0.002.	II	Perren 2011[14]
In ICON7, bevacizumab treatment was associated with a small but clinically significant decrease in quality of life compared to standard chemotherapy.	II	Stark 2013[54]
In the GOG 218 trial, progression-free survival was improved in the bevacizumab throughout arm (chemotherapy plus bevacizumab cycles 2 to 22) (p= <0.001), but not in the bevacizumab initiation arm (chemotherapy plus bevacizumab cycles 2 to 6), compared to the chemotherapy control group.	II	Burger 2011[15]
In GOG 218, in both arms concurrent bevacizumab compared to control without bevacizumab, doubled the odds of a gastrointestinal adverse event (odds ratio 2.15, 95% CI 1.05-4.40, p=0.032), after controlling for history of treatment for irritable bowel disease, small bowel resection at primary surgery and bowel resection at primary surgery, however was not appreciably increased by continuation of bevacizumab beyond chemotherapy.	II	Burger 2014[55]

Scheduling – Dose-dense chemotherapy

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
In one trial (JGOG 3016), dose-dense paclitaxel improved overall survival at 5 years (58.6% vs. 51.0%, HR 0.79, p=0.0448) and median progression-free survival at median 6.4 years follow-up (28.1 vs. 17.5 months, HR 0.75, p=0.0037) in women with advanced ovarian cancer compared with standard treatment. Anaemia was worse in the dose-dense arm but no significant	II	Katsumata 2009[47] Katsumata 2012[48]

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STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
differences were reported for other toxicities.		
In two trials that investigated complex, high-dose chemotherapy regimens including peripheral blood stem cell support, no overall or progression-free survival differences were reported between intervention and standard treatment arms.	II	Grenman 2006[56] Mobus 2007[57]

Scheduling – Intraperitoneal Chemotherapy

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
A meta-analysis has indicated that women with epithelial ovarian cancer who received an intraperitoneal component of chemotherapy had significantly better overall survival HR 0.81, p=0.0002 and progression-free survival HR 0.78, p<0.00001, than women who did not.	I	Jaaback 2011[45]
Women receiving intraperitoneal chemotherapy were significantly more likely to experience a range of adverse events, including gastrointestinal effects, pain, fever and infection.	I	Jaaback 2011[45]

Scheduling – Neoadjuvant Chemotherapy

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
One randomised trial has indicated no differences in median overall survival between treatment arms for women receiving neoadjuvant chemotherapy compared with primary surgery.	II	Vergote 2010[44]
Subgroup analyses by age, FIGO stage, WHO performance status, histologic type and presence or absence of pleural fluid demonstrated no survival differences between neoadjuvant chemotherapy and primary surgery arms.	II	Vergote 2010[44]
More adverse events were observed in the primary surgery arm compared with women receiving neoadjuvant chemotherapy.	II	Vergote 2010[44]

BRCA mutations

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
BRCA mutation carriers were more likely to have a complete or partial response to platinum-based chemotherapy than non-carriers or sporadic cases.	III-2	Yang 2011[58] Vencken 2011[59] Tan 2009[60]
Women with a BRCA1/2 mutation receiving a platinum-based regimen were less likely to have disease progression within 6 months of the end of primary treatment compared with those who did not carry a BRCA1/2 mutation; 14.9% vs. 31.7%, p<0.001.	III-2	Alsop 2012[61]

Older women

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
Improved survival was reported in women aged 65 years and older who received chemotherapy compared with those who had no chemotherapy (RR 0.59).	III-2	Hershman 2004[62]
In a study of women with median age 73 years, overall survival and progression-free survival were improved in women receiving carboplatin or a combination of platinum and paclitaxel compared with those receiving a non-platinum regimen.	II	Reed 2006[25]
Women aged 70 years and over discontinued their treatment earlier than those aged under 70 years (p=0.001).	III-3	Hilpert 2007[63]
In the OVAR trial, most haematological toxicity did not differ between age groups; however, febrile neutropenia was more frequent in older patients than in younger patients (p <0.001). There were no significant differences in non-haematological toxicity between age groups, except that older patients were more likely to get grade 3/4 infections.	III-3	Hilpert 2007[63]

Obese patients

STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
While the evidence indicates that obese women are under dosed and have inferior survival, the available evidence is limited. No studies were identified which specifically compared different doses of chemotherapy among obese patients for survival outcomes. • In four studies there were no statistically significant differences in overall survival, progression-free survival or disease free survival across the BMI strata.	III-3	Wright 2008[64] Barrett 2008[65] Matthews 2009[66] Suh 2012[67]
• In only one study (SCOTROC) the taxane dosage was not capped.	III-3	Barrett 2008[65]
• One study reported that, compared to non-obese patients, obese patients had a lower recurrence rate (68% vs. 79%, p=0.04) but no statistically significant difference in progression-free survival. Dosage was based on their current body weight and BSA (Body surface area) capped at 2.0 m^2.	III-3	Matthews 2009[66]
• One retrospective study demonstrated delivered relative dose intensity (RDI) <85% to be negatively associated with overall survival; multivariate analysis: HR=1.71, p=0.003. BSA greater than 2m^2 and BMI >30 kg/m^2 were reported to be predictors of reduced planned RDI <85% and reduced delivered RDI <85%.	III-3	Hanna 2013[68]
• In one retrospective study, in which patients who were obese were more likely to receive a lower median dose of paclitaxel relative to BSA compared to those of ideal body weight, increasing BMI was associated with lower overall survival.	III-3	Pavelka 2006[69]
• One retrospective study reported there was no significant difference between BMI groups for overall or progression-free survival. However, patients receiving RDI <85% for carboplatin had worse progression-free survival; univariate analysis HR 1.29, p=0.04. Multivariate analysis was not significant.	III-3	Au-Yeung 2014[70]
In one retrospective analysis, where the average dose of carboplatin received did not differ across the BMI strata, obese women were less likely to experience treatment-related toxicity.	III-3	Wright 2008[64]
A retrospective study of adverse events reported that a BMI<30 and BSA <2.0m^2 were univariate predictors of severe neutropenia in women with stage III and IV undergoing a multi-agent intravenous chemotherapy (p=<0.01 and p=0.03).	III-3	Laskey 2012[71]

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STATEMENTS	LEVEL OF EVIDENCE[11]	REFERENCE
One study reported similar rates of neutropenia for obese and non-obese patients.	III-3	Matthews 2009[66]

Summary of evidence

The statements of evidence and recommendations about the use of first-line chemotherapy for epithelial ovarian cancer are based on a Cancer Australia systematic review of available evidence published between January 2003 and November 2012.[9]

This systematic review was undertaken by Cancer Australia to identify any revisions required to recommendations for chemotherapy and ensure currency of the 2004 guidelines. Following consultation with a multidisciplinary working group, it was agreed that the scope of the review would be limited to first-line treatment of epithelial ovarian cancer, given differing treatment modalities and heterogeneous needs of women with recurrent disease.

A search of the literature published between January 2003 and March 2012 was undertaken using electronic databases. The primary search was limited to randomised controlled trials (RCTs) conducted in humans published in the English language. A supplementary search was conducted to identify articles on subsets of the defined population that have specific chemotherapy requirements; this search was not limited to RCTs and included additional search terms related to the sub-populations. In October 2012 the multidisciplinary working group re-prioritised the other issue of obese patients to be a research question. The new research question was systematically searched for in November 2012.

Overall, 75 articles and two conference abstracts were included in the systematic review. Of the included citations, 35 were phase III (RCTs) addressing the primary research questions, 10 were non-randomised controlled trials included in the sub-group question and six were Cochrane reviews used as primary references.

The systematic review addressed six research questions which were developed with input from the multidisciplinary working group. The questions addressed were:

1. What is the most effective chemotherapy regimen for first-line adjuvant treatment of epithelial ovarian cancer?
2. What is the most effective schedule (duration/dose/frequency) for chemotherapy regimens for first-line adjuvant treatment of epithelial ovarian cancer?
3. What is the most effective mode of administration for chemotherapy regimens for first-line adjuvant treatment of epithelial ovarian cancer?
4. When is the most effective time to administer chemotherapy for first-line treatment of epithelial ovarian cancer?
5. Are there subsets of the defined population for first-line adjuvant treatment of epithelial ovarian cancer (such as women with BRCA mutations) that have specific chemotherapy requirements?
6. What are the specific chemotherapy requirements for women with epithelial ovarian cancer who are obese?

The following topics were considered as additional issues of interest, and although they were not specifically searched for in the systematic review, any information on these topics identified was recorded:

- Any other women with specific chemotherapy requirements/issues for example rural/remote, Aboriginal

and Torres Strait Islander women.
- Resources specification, for example: resources required for intraperitoneal chemotherapy.
- Patient selection criteria.

For detailed evidence from studies on the use of first-line chemotherapy for epithelial ovarian cancer refer to the [Cancer Australia systematic review](#)[9].

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Summary of study results

Chemotherapy regimens for first-line adjuvant treatment

Early stage ovarian cancer (FIGO stage I-IIa)

Overall survival

While meta-analysis of five-year data from three trials, and of ten-year data from two trials, indicated that women who received adjuvant platinum-based chemotherapy had better overall survival (OS) than those who did not, subgroup analysis suggested that women who had comprehensive surgical staging of their disease were unlikely to benefit from adjuvant chemotherapy, whereas those who had sub-optimal staging did.[13]

One trial included in the Cochrane Review (ICON 1) reported overall survival grouped by level of risk, with low/medium risk, defined as stage 1a, tumour grade 1 and 2, stage 1b or 1c, grade 1; high risk was defined as stage 1a, grade 3, stage 1b or 1c grade 2 or 3, any clear cell tumours. In the low and medium risk group, there was no significant difference in 10-year overall survival between those who received adjuvant chemotherapy and those who received surgery alone. However, among women at high risk, adjuvant chemotherapy improved survival HR 0.48 (95% CI 0.32 to 0.72), p=0.00039.[13]

Analysis of data from 693 women in three trials, showed no significant difference in deaths from ovarian cancer at five years, between the chemotherapy and observation groups (RR 0.76, 95% CI 0.52 to 1.11). Only one RCT (ACTION) reported 10-year follow-up for this outcome, with no significant difference in deaths from ovarian cancer between the two groups overall. Significantly fewer deaths occurred in the chemotherapy arm of the sub-optimally staged subgroup. However, there was no difference for those in the comprehensively staged subgroup.[13]

Progression-free survival

Among comprehensively staged women, analysis showed no significant difference in progression-free survival (PFS) between those who did and did not receive adjuvant chemotherapy. However, in sub-optimally staged women, those receiving adjuvant chemotherapy had significantly better PFS than those who did not.[13]

ICON 1 reported progression-free survival grouped by level of risk. The 10-year progression-free survival between adjuvant chemotherapy compared with observation was not significantly different among women at low and medium risk. However in women at high risk, adjuvant chemotherapy improved PFS HR 0.52 (95% CI 0.33 to 0.82), p=0.0049.[13]

None of the trials reported on treatment compliance, response to chemotherapy, adverse events or quality of life.

Ovarian cancer (stage I-IV) - Chemotherapy

A range of regimens have been investigated, most of which were compared with the combination of carboplatin and paclitaxel (considered as standard first-line chemotherapy). The type of comparison was usually a substitution of different agents or the addition of a third agent. Various platinum/taxane combinations were compared. Additional agents investigated included anthracyclines (doxorubicin, epirubicin), antimetabolites (gemcitabine), and topoisomerase inhibitors (topotecan, irinotecan.)[14-43, 72]

Almost all the regimens failed to demonstrate an overall or progression-free survival benefit compared with standard chemotherapy (most often platinum/taxane combination). Trials which did show survival differences were either in specific patient populations or compared older chemotherapy regimens no longer considered standard.

Overall survival

A multiple-treatment modelling meta-analysis reported hazard ratios for death for first-line treatment, for each type of regimen compared with monotherapy with a non-platinum, non-taxane agent, not administered intraperitoneally. Modelling estimated a 92% probability that combinations of platinum and taxane with intraperitoneal administration were the most effective regimens.[72]

Two phase III trials reported differences in overall survival. The trial by Reed et al (2006), which included patients unfit to receive cisplatin, reported improved survival in the carboplatin arm (median 15 months) compared with treosulfan (median 12 months) ($p<0.026$).[25] Long-term follow-up of the OV10 trial of older chemotherapy regimens, reported that paclitaxel and cisplatin combination improved survival compared with cyclophosphamide and cisplatin HR 0.75 (95% CI 0.63 to 0.90), $p=0.001$.[35]

Progression-free survival

Twenty-three of the primary randomised controlled trials reported on progression-free survival. One trial reported on disease-free survival rather than progression-free survival.[24] Most reported no statistically significant progression-free/disease-free survival differences between treatment groups however, the phase II trials were not designed/powered to detect survival differences.

Three phase III trials reported differences in progression-free survival: Reed et al (2006), OV10[35] and OVAR9.[17]
 In two trials, those in the standard chemotherapy arm had longer progression-free survival than those in the intervention arm. The trial by Reed et al (2006) reported longer time to progression in the carboplatin arm (10 months) compared with treosulfan (5 months) ($p<0.001$).[25] The OVAR9 trial reported median progression-free survival in the standard paclitaxel/carboplatin arm as 19.3 months compared with 17.8 months for the paclitaxel/carboplatin/gemcitabine arm ($p<0.01$).[17]

In the other trial, improved progression-free survival, was reported in the intervention arm. OV10 reported better PFS in the paclitaxel/cisplatin arm compared with the older chemotherapy regimen cyclophosphamide/cisplatin ($p<0.001$).[35]

Adverse events

The adverse events reported varied between each trial. Overall, the addition of agents to standard chemotherapy tended to increase toxicity, particularly haematological toxicity such as anaemia and neutropenia. Adverse effect profiles reflected the various agents used. However, there were often limited differences in toxicities between treatment arms.

Quality of life

Quality of life (QoL) was assessed in 13 trials, with detailed data reported in 11 trials. Most trials reported no significant differences in quality of life between treatment arms investigated.[28, 29, 31] OVAR 3 found that those in the carboplatin/paclitaxel arm showed better overall QoL, physical functioning, role functioning, and cognitive functioning compared with those in the cisplatin/paclitaxel arm after treatment.[30] However, an additional paper which reported a retrospective analysis of data from OVAR 3, OVAR 5 and OVAR 7 found that correlations between toxicity grading and quality of life functioning scales were weak and symptom level agreement between clinician and patient reporting could differ.[30]

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Ovarian cancer (stage I-IV) - Biological therapies

Based on a study of molecular pathways involved in tumour growth, a number of potential anti-angiogenic agents have been identified. Bevazicumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has been studied in the first-line treatment of ovarian cancer.[73]

The ICON7, a phase III randomised study, compared standard chemotherapy (carboplatin AUC 5 or 6 and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles) or standard chemotherapy plus bevacizumab (7.5 mg per kilo body weight) given concurrently every 3 weeks for 5 or 6 cycles and continued for 12 additional cycles or until progression of disease.[14]

GOG 218, a double-blind phase III randomised controlled trial compared three treatments. Each of the three study regimens comprised 22 3-week cycles paclitaxel 175 mg/m^2 plus carboplatin AUC 6. **Control** treatment was chemotherapy with placebo added in cycles 2 through 22; **bevacizumab initiation treatment** was chemotherapy with bevacizumab (15 mg per kg body weight) added in cycles 2 through 6 and placebo added in cycles 7 through 22. **Bevacizumab-throughout treatment** was chemotherapy with bevacizumab added in cycles 2 through 22. [15]

Overall survival

The ICON7 trial reported that there were no overall survival differences between treatment groups. However, improved survival was reported in a subgroup of patients (n=465) at high risk of progression (stage IV disease or stage III and >1 cm residual disease) in the bevacizumab (7.5 mg/kg body weight) plus standard therapy (carboplatin + paclitaxel) group, compared to the standard therapy alone group.[14] Patients in the bevacizumab arm had improved survival OS median 36.6 months in intervention group, 28.8 months in control group, HR 0.64 (95% CI 0.48 to 0.85), p=0.002.[14]

In the GOG 218 trial, bevacizumab (15 mg/kg body weight) was given every three weeks, in addition to the standard carboplatin/paclitaxel regimen. No significant differences in overall survival were reported between the three groups (bezacizumab-initiation group, bezacizumab-throughout group and control group).[15]

Progression-free survival

In the updated analyses from ICON7, improved progression-free survival, (19.8 months vs. 17.4 months; p=0.04), was reported in the group receiving bevazicumab (7.5 mg/kg of body weight), compared with standard therapy.[14] The maximum improvement was at 12 months, co-inciding with the end of planned bevacizumab treatment, and diminished by 24 months. Median PFS in the updated analyses was 16 months in the bevacizumab group compared with 10.5 months in the standard therapy group (p=0.002).[14]

In GOG2018, progression-free survival was improved in the bevacizumab throughout arm (median 14.1 months) compared with control (median 10.3 months) (p<0.001), however this improvement was not observed in the bevacizumab initiation arm (median 11.2 months) (p=0.16).[15]

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Adverse events

In GOG 218, in both arms concurrent bevacizumab compared to control group without bevacizumab, doubled the odds of a gastrointestinal adverse event (odds ratio 2.15, 95% CI 1.05-4.40, p=0.032), after controlling for history of treatment for irritable bowel disease, small bowel resection at primary surgery and bowel resection at primary surgery, however was not appreciably increased by continuation of bevacizumab beyond chemotherapy.[55]

Quality of life

In ICON7, bevacizumab treatment was associated with a small but clinically significant decrease in quality of life compared to standard chemotherapy.[54]

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Scheduling

Dose-dense therapy

Dose-dense chemotherapy, where the interval between chemotherapy cycles is reduced, has been considered to improve the activity of drugs used to treat ovarian cancer.[73] Dose-dense chemotherapy reduces the time for tumour re-growth between cycles.[74] The cumulative drug dose remains constant but the same amount of drug is administered over a shorter period of time.[74]

In an RCT conducted in Japan (JGOG 3016) 637 patients with FIGO stage II-IV disease were randomly assigned to receive paclitaxel (80 mg/m^2) once weekly and carboplatin every three weeks (dose-dense therapy) or carboplatin (AUC6)and paclitaxel 180 mg/m^2 given every three weeks (standard therapy).[48]

Overall survival

Dose-dense paclitaxel improved overall and progression-free survival compared to the standard treatment. Overall survival at two and three years was significantly better in the dose-dense paclitaxel arm compared to the standard dose arm (2 yrs: 83.6% vs. 77.7%, p=0.049; 3 yrs: 72.1% vs. 65.1%, p= 0.03). At five years, OS was higher in the dose-dense group 58.6% vs. 51.0%, HR 0.79, 95% CI 0.63-0.99, p=0.0448). At 6.4 years of median follow up, median survival had not been reached in the dose-dense group.[47]

Progression-free survival

JGOG 3016 also reported improved progression-free survival. Median progression-free survival was 28 months in the dose-dense paclitaxel arm, compared with 17.2 months in the standard arm, adjusted HR 0.65, (95% CI 0.53 to 0.80), p = 0.0001. PFS was longer in the dose-dense arm across all sub-groups, except amongst women with clear-cell or mucinous tumours.

Adverse events

Sixty-two percent (62%) of patients in the dose-dense arm received six or more cycles compared to 73% in the standard arm. The most common adverse event was neutropenia (dose-dense regimen, 286 [92%] of 312; conventional regimen, 276 [88%] of 314). The frequency of grade 3 and 4 anaemia was higher in the dose-dense treatment group (214 [69%]) than in the conventional treatment group (137 [44%]; p<0.001). The frequencies of other toxic effects were similar between groups.

Quality of life

A 2014 publication of the JGOG 3016 trial by Harano et al, reported QoL outcomes. QoL was assessed at baseline, 6 months and 12 months using FACT-general scale, FACT-taxane subscale and FACT-ovary subscale. The authors reported no significant difference in QoL between the two treatment groups up to 12 months after randomisation (p=0.46). However, QoL was significant lower in the dose-dense group according to the

FACT-taxane subscale, compared with the conventional chemotherapy group (p=0.02).[49]

Dose-dense chemotherapy has been adopted in some centres. However, given that JGOG 3016 involved patients recruited only in Japan (mostly stage III) and that patients who had treatment delays or neutropenic complications received granulocyte-colony stimulating factor (G-CSF), a number of international trials (including the Italian trial MITO7, ICON8 AND GOG 262) are in progress to further assess the applicability of dose-dense regimens for other populations.[73]

Complex high-dose chemotherapy regimens

In two trials that investigated complex high-dose chemotherapy regimens including peripheral blood stem cell support, no overall or progression-free survival differences were reported between the intervention and standard treatment arms.[56, 57]

Intraperitoneal (IP) chemotherapy

A Cochrane systematic review published in 2011, included RCTs published up to May 2011 on IP chemotherapy.[45] Only one of the nine trials (Kirmani 1994) directly compared intravenous (IV) to IP (without additional IV) chemotherapy; the remaining trials compared administered a certain component of chemotherapy via IV or IP, along with IV chemotherapy in both arms. The chemotherapy component administered IP always included a platinum agent, usually cisplatin, with or without additional agents. The IV chemotherapy given to both arms usually included paclitaxel or cyclophosphamide.[45]

Overall survival

The Cochrane review reported significantly improved overall survival for women who received an IP component of chemotherapy.[45] From meta-analysis of data from eight studies (2026 women) for overall survival, the hazard ratio was 0.81 (95% CI 0.72 to 0.90), p=0.0002 for women who received an IP component of chemotherapy compared to only IV chemotherapy. Results were similar when only data from the six high quality trials was used: HR 0.80 (95% CI 0.72 to 0.90), p=0.0001 and when the analysis was restricted to trials that used the same chemotherapy regimens in each arm (data from 3 studies: HR 0.79 (95% CI 0.67 to 0.92)).[45]

Progression-free survival

The Cochrane review reported significantly improved progression-free survival for women who received an IP component of chemotherapy.[45] From meta-analysis of five studies (1311 women) the hazard ratio was 0.78 (95% CI 0.70 to 0.86), p<0.00001. The data were reported to be homogenous.

Adverse events

The Cochrane review reported that women in the IP chemotherapy groups were significantly more likely to

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experience severe adverse effects (grade 3/4): fever (RR 1.64), fatigue (RR 2.32), gastrointestinal adverse events (RR 1.70), infection (RR 3.34), metabolic adverse events (RR 4.45) and pain (RR 7.47).[45] Hearing loss was more common in the IV chemotherapy groups (RR 0.67). There were no significant differences between interventions for haematological adverse events (such as anaemia, thrombocytopenia and leukopenia), renal, neurological and pulmonary adverse events.[45] However, substantial heterogeneity was noted in these meta-analyses.

Insufficient data were available for meta-analysis of catheter-related complications of IP drug administration, including infection, blockage and discontinuation of therapy.

Treatment compliance

An additional paper was identified in the Cancer Australia literature review which investigated factors affecting the completion of IP chemotherapy in women with ovarian cancer.[75] The study included 140 patients from one US centre who received IP chemotherapy as initial treatment; some of these were part of the GOG 172 trial as well as other IP chemotherapy trials.

Of these 140 patients, 95 (68%) completed all six planned cycles of treatment.

The reasons for non-completion of the planned regimen included:

- Occlusion of the port (28 patients, 20%)
- Progression of disease (7 patients, 5%)
- Refusal by the patient to accept further IP treatment (6 patients, 4%)
- Infection of the port/port site (3 patients, 2%)
- Rupture of the port tubing (1 patient, <1%).[75]

Quality of life

Only GOG 172 assessed quality of life (QoL) as an outcome measure. Women who received higher dose IP therapy experienced more QoL disruption compared to those who received IV therapy. Those in the IP arm reported worse QoL and pain prior to the fourth chemotherapy cycle and worse QoL three to six weeks post-treatment. However, there were no significant QoL or PAIN score differences between arms at one year post-treatment.

Neoadjuvant chemotherapy

One randomised controlled trial (EORTC 55971) was identified that compared neoadjuvant chemotherapy with primary surgery followed by adjuvant chemotherapy.[44] The trial included 670 women from 59 institutions with stage IIIC or IV invasive epithelial ovarian cancer, primary peritoneal or fallopian tube cancer, with extensive disease (61% metastases >10 cm at primary debulking).[44, 76] Most (76%) of the included patients had stage IIIC ovarian cancer. The median age range was 62-63 (range 25-86) and the majority of patients had serous histology (62%).

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The trial randomised women to either:

i. Three courses of neoadjuvant platinum-based chemotherapy followed by debulking surgery in all patients with a response or stable disease, followed in turn by at least three courses of platinum-based chemotherapy (n=334)

or

ii. primary debulking surgery followed by at least six courses of platinum-based chemotherapy (n=336).[44]

Optimal resection with no macroscopic residual tumour was achieved in 19% of cases after primary debulking and in 51% after interval debulking. However, debulking rates differed from country to country in this international trial.[76]

The most common chemotherapy regimen was paclitaxel (175mg/m2) plus carboplatin (AUC6). Eighty-six per cent of patients in the neoadjuvant chemotherapy group received at least six cycles of chemotherapy compared with 82% in the primary surgery group. Around 7% of patients in the primary surgery group received no chemotherapy, mainly due to post-surgery complications or the diagnosis of another primary tumour, while 88% of patients in the neoadjuvant group underwent interval debulking surgery.[44]

Overall survival

The trial found no difference in the median overall survival between the two groups (median 30 months in the neoadjuvant chemotherapy group compared with 29 months in the primary surgery group, HR 0.98 (90% CI 0.84 to 1.13)).[44] Subgroup analyses by age, FIGO stage, WHO performance status, histologic type, and presence or absence of pleural fluid showed no survival differences between the treatment groups. The only difference reported was that neoadjuvant chemotherapy appeared to improve survival among patients with metastatic tumours that were less than 5 cm in diameter at randomisation (HR 0.64 (95% CI 0.45-0.93)).[44]

Progression-free survival

The trial reported no difference in the median progression-free survival between the two groups (median 12 months in neoadjuvant chemotherapy group compared with 12 months in primary surgery group, HR 1.01 (90% CI 0.89 to 1.15)).[44]

Adverse events

There was a higher percentage of post-operative deaths (<28 days after surgery) in the primary surgery group (2.5%) compared with neoadjuvant chemotherapy (0.7%) (statistical significance not reported).[44] Grade 3 or 4 haemorrhage, infections and venous complications were worse in the primary surgery group compared with the neoadjuvant chemotherapy group (statistical significance not reported).[44] Direct statistical comparison was not possible as post-operative morbidity and mortality in the primary chemotherapy group could only be analysed in the 92% of patients who underwent interval debulking; the remaining 8% either died or had disease progression and may have selected out poor-risk patients who were included in the post-operative analysis after primary cytoreduction.[76]

Quality of life

Quality of life was assessed using the EORTC QLQ-C30. The trial reported no significant differences between groups in the QLQ-C30 global health scores at any of the assessment times. The overall test for a treatment effect on global health was also not significant.[44]

Additional studies of interest

The CHORUS trial (CRUK 07/009), a randomised controlled trial investigating neoadjuvant chemotherapy, has reported outcomes in a conference abstract.[77] Patients with clinical FIGO stage III-IV ovarian cancer were randomised to standard treatment (n= 276; primary surgery followed by six cycles of platinum-based chemotherapy) or neoadjuvant chemotherapy (n= 274; three cycles platinum-based chemotherapy either side of surgery). The median age was 65 years, median tumour size was 80mm and 25% of patients were FIGO stage IV.

At median follow-up of three years, intention to treat analysis showed a median overall survival of 22.8 months for primary surgery vs 24.5 months for neoadjuvant chemotherapy (hazard ratio (HR) 0.87 in favor of neoadjuvant chemotherapy, 80% CI 0.76 – 0.98) and median progression free survival of 10.2 vs 11.7 months (HR 0.91, 0.81 – 1.02). The 12-month survival rates were 70% for primary surgery and 76% for neoadjuvant chemotherapy. For patients treated with primary surgery, 15% were debulked to 0cm residual disease, compared to 35% for neoadjuvant chemotherapy.[77]

A small, phase II trial of 83 women (PRIMOVAR) reported no differences in outcomes between women receiving three cycles of neoadjuvant chemotherapy versus two cycles prior to surgery.[78]

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BRCA mutations

Limited information was identified to suggest that there are specific chemotherapy requirements for BRCA carriers. Three studies that investigated the relationship between BRCA status and the effectiveness of chemotherapy, did not report on the impact of chemotherapy on overall or progression-free survival, treatment compliance, adverse events or quality of life, but did report on response to chemotherapy.

The study by Alsop et al published after the systematic search, investigated the frequency of BRCA mutations and patterns of treatment response in a prospectively ascertained population-based cohort of 1001 Australian women with newly diagnosed non mucinous ovarian cancer.[61] Germ-line pathogenic BRCA1 or BRCA2 mutations were identified in 141 (14.1%) of the women. Of the 837 patients who received chemotherapy during primary treatment, 835 (99.8%) received a platinum-based regimen and 642 (76.9%) received carboplatin/paclitaxel. Patients with BRCA1 and BRCA2 mutations were less likely to have disease progression within six months of the end of primary treatment compared with those not carrying mutations (14.9% vs. 31.7% respectively, p<0.001). Disease progression within six months of completing primary platinum-based chemotherapy has conventionally been associated with platinum resistance.[61]

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Older Women

There is a lack of prospective randomised trial data specifically in older populations.

While the majority of trials in the systematic review did not impose an age limit, the median age was most often between 55 and 60 years. Of those trials that did impose an age limit, two trials included patients up to 65 years, one up to 70 years and one up to 80 years.

It is recognised that older women with ovarian cancer have more aggressive tumours, more advanced stage at diagnosis, increased risk of death from their cancer and more comorbidities than younger patients.[79] Data from an Australian population-based study also indicate that patients over the age of 70 years are less likely to receive standard chemotherapy.[80]

The current standard chemotherapy regimen of three weekly carboplatin and paclitaxel is generally well tolerated and has established efficacy in older patients.[50] Despite this, alternative strategies such as using single agent carboplatin, reducing the dose and weekly scheduling are used in an attempt to preserve efficacy and reduce toxicity. These therapeutic manoeuvres are based on small phase II trials or retrospective analyses.

In a retrospective analysis of a large prospective trial (GOG182) it was shown that older patients (age > 70 years) were less likely to complete the prescribed 8 cycles of chemotherapy, had a shorter survival and increased toxicity; particularly peripheral neuropathy and bone marrow suppression. These data are published in abstract form only, but this is currently the largest age-specific subgroup analysis of a prospective trial.[81] Unfortunately, this subgroup is probably not representative of the wider population of elderly women requiring treatment for ovarian cancer. Prospective trials of chemotherapy in older women are required particularly in patients who are frail or have comorbidities.

The National Comprehensive Cancer Network (NCCN) guidelines for management of cancer in the senior adult contain a specific section on the management of ovarian cancer.[82] These guidelines also stress the importance of adequate geriatric assessment that then informs appropriate treatment decisions and guides supportive care for both the patients and their carers. Assessment tools based on factors including functional status, comorbidities, cognitive function and nutritional status can assist a comprehensive geriatric assessment.[82]

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Histological sub-types

The majority of ovarian cancer patients are diagnosed with serous carcinomas (80-85%) and these tumours have a high response rate to platinum-based chemotherapy.[73] While one sub-set analysis in the ACTION trial showed improved overall survival for women with early-stage ovarian cancer within the chemotherapy arm, for those with serous carcinoma compared with clear-cell carcinoma (p= 0.04), the differences disappeared when optimal staging was taken into account.[83]   The sub-set analysis also showed adjuvant chemotherapy significantly improved disease-free survival for women with serous ovarian cancer but there was no significant improvement for women with clear-cell ovarian cancer.

Analysis of data from four randomised phase III and one phase II first-line trials (GINECO database) indicated that women with mucinous ovarian cancer receiving carboplatin-paclitaxel based chemotherapy had significantly lower overall response (complete and partial) (p<0.001), shorter overall survival and shorter progression-free survival than women who had serous ovarian cancer.[84]

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Obese patients

The American Society of Clinical Oncology (ASCO) published clinical practice guidelines on the appropriate chemotherapy dosing for obese adult patients with cancer in 2012.[51] These guidelines were not specific to ovarian cancer, however the guidelines noted that a majority of studies identified in the systematic review for the guidelines involved breast, ovarian, colon and lung cancers. The ASCO guidelines recommend that full weight-based cytotoxic chemotherapy doses be used to treat obese patients with cancer, particularly when the goal of treatment is cure.(ASCO: **http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.39.9436**)

No studies were identified which specifically compared different doses of chemotherapy among obese patients for survival outcomes.

Nine studies were identified which included obese patient populations and compared outcomes by BMI or by obesity. In most of the studies, chemotherapy dosing was based on actual body weight, whereas in some studies the formula used did not include body weight or body surface areas (BSA). Six of the studies examined the impact of BMI on outcomes including survival and adverse events.[64-69] Three of the studies reported on adverse events and BMI only.[71, 85, 86]

Hourdequin et al (2013) published a systematic review and meta-analysis of studies comparing toxic effect and survival outcomes between obese and normal weight cancer patients. Patients in the studies were from various tumour groups. Both obese and normal weight patients received chemotherapy dosed using actual body weight, without dose reductions. The authors concluded that obese patients receiving chemotherapy based on actual body weight experienced similar or lower rates of toxic effects as normal weight patients, and survival outcomes do not differ.[87]

An additional study published in 2014 was also identified. Au-Yeung et al (2014) published a retrospective study from the Australian Ovarian Cancer Study (AOCS) to evaluate the relationship between BMI, dose intensity of chemotherapy received, overall survival and progression-free survival. Doses were calculated based on standard treatment regimen.[70]

Survival

No significant differences in overall, progression-free or disease-free survival were reported between obese and non-obese patients in most of the studies. One study SCOTROC I, (Barrett et al, 2008) did not find a link between obesity and poorer prognosis, with the authors noting this finding was due to more accurate dose calculations in that study.[65] The authors recommended accurate measurement of GFR and chemotherapy doses based on actual body weight rather than ideal body weight.

Au-Yeung et al (2014) reported no significant association between BMI groups and overall or progression-free survival. Patients who received less than 85% RDI for carboplatin had significantly worse progression-free survival (univariate analysis: median PFS 11 vs. 15mths; p=0.04). In multivariate analysis, the difference in progression-free survival for RDI of carboplatin trended in the same direction but no longer reached statistical significance (p=0.06).\

Dosing

The majority of studies reported similar numbers of lines, courses, number of platinum-based regimens of chemotherapy between obese and non-obese patients. One study (Hanna et al 2013) determined BSA greater than $2m^2$ and BMI >30 kg/m^2 to be predictors of reduced planned relative dose intensity (RDI) <85% and reduced delivered RDI <85%.[68]

Wright et al (2008) reported that over the entire treatment course, the average dose of carboplatin received during treatment did not differ across BMI strata.[64]

Data from the SCOTROC I trial, showed no statistically significant differences overall between the two arms for dose intensity or cumulative dose. In the current study of 1067 patients who received taxane treatment and had recorded BMI, there was neither a statistically significant difference in taxane dose intensity (p=0.120) nor carboplatin dose intensity (p=0.578) between the BMI categories.[65] There was also no statistically significant difference between total intended taxane dose (p=0.217) or total intended carboplatin dose (p=0.722) between BMI categories. Based on the findings of no significant differences in survival between BMI categories from this study, in which chemotherapy dose was based on measured GFR, the authors suggested accurate measurement of GFR before commencing chemotherapy and chemotherapy doses based on actual body weight.[65]

In the study by Suh et al. (2012), there were no significant differences across BMI categories for the number of lines of chemotherapy used, the number of courses of chemotherapy or the number of courses before recurrence.[67] The level of neutropenia and platinum sensitivity rate were also similar in BMI groups.

Au-Yeung et al (2014) reported that obese patients were more likely to receive RDI <85% for carboplatin compared to non-obese patients (p<0.001). The RDI comparison for paclitaxel was not significantly different between BMI groups (p=0.76). For the average RDI for both carboplatin and paclitaxel, significantly more obese patients received an average RDI <85% (p=0.02).

Adverse events

Adverse events reported, and any differences between BMI groups, varied between studies. In the study by Wright et al, in which the carboplatin dose calculation did not adjust for body weight, obese women were reported to experience less treatment-related toxicity compared with normal weight subjects.[64] The authors suggested that as obese women were less likely to experience treatment-related toxicity, these women received a lower effective dose of carboplatin and that body weight should be taken into consideration when calculating carboplatin dose.[64]

Matthews et al (2009) reported similar rates of neutropenia for obese and non-obese patients (52% and 46%, p=0.39).[66]

In the Japanese study by Sendo et al (2005) a multivariate analysis demonstrated that the incidence of hypersensitivity reactions to paclitaxel was significantly higher in obese patients (BMI >25)(OR 8.47, 95% CI 1.48-48.57, p=0.017).[86]

Laskey et al (2012) reported that BMI <30 and BSA <2.0 m^2 were significant predictors of severe neutropenia in women with stage III and IV epithelial ovarian cancer by univariate analysis (p=<0.01 and p=0.03).[71] Multivariate analysis indicated a trend to an association between severe neutropenia and BMI <30 (HR 1.60, p=0.06).

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Additional issues of interest

Specific chemotherapy requirements/issues for women in rural/remote areas, Aboriginal and Torres Strait Islander women, resources specification, and patient selection criteria were considered as additional issues of interest. No information about these issues was recorded from the search.

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Strengths and weakness of the evidence

The evidence included in the systematic review was primarily based on randomised controlled trials. The quality of all included systematic reviews and randomised controlled trials was considered to be moderate to high.

Thirty-five randomised controlled trials were included in the systematic review for the primary research questions:

- Each of the included trials was considered to be of moderate to high quality.
- The trials were all randomised, though some trials did not describe randomisation method. In trials that did specify method of randomisation, methods were considered high quality.
- The trials were either open label or blinding was not stated, with only GOG218 identified as double blind.
- Survival outcomes by intention-to-treat analysis were reported by the majority of trials.
- All trials had standardised assessment of outcomes and almost every trial had well matched population characteristics between treatment arms at baseline.
- Most of the phase III trials were powered to detect a significant difference in primary outcomes.

Ten studies that were not randomised controlled trials were included for the research question assessing subgroups. As the papers included in this section had a range of study designs, formal quality assessment was not performed.

Nine studies that were not randomised controlled trials were included for the research question addressing specific chemotherapy requirements for women with epithelial ovarian cancer who are obese. These studies did not compare different doses or schedules of chemotherapy among obese patients.

Six Cochrane reviews were included in the systematic review. These were considered to be of high quality.

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Unanswered questions

Important unanswered questions about the use of first-line chemotherapy for the treatment of women with epithelial ovarian cancer may be addressed in clinical trials investigating:

- Generalisability of dose-dense chemotherapy across a range of populations.
- Role of novel biological/molecular therapies in the first-line treatment of women with epithelial ovarian cancer.
- Chemotherapy regimens in older women, particularly in patients who are frail or have comorbidities.
- Specific chemotherapy requirements for women with epithelial ovarian cancer who are obese.

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International clinical practice guidelines

Five international guidelines regarding the management of ovarian cancer in general were identified. Recommendations with regards to chemotherapy are provided in the [Cancer Australia systematic review](#), Appendix F.[9]

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Ongoing trials

Clinical trials are an important way to improve treatment for people with cancer. The results of clinical trials today will help people with cancer in the future. Participating in a clinical trial may be of direct benefit to women with epithelial ovarian cancer. For more information about clinical trials visit Australian Cancer Trials at http://www.australiancancertrials.gov.au/

There are a number of trials investigating the first-line chemotherapy for women with epithelial ovarian cancer. A summary of trials is outlined in the Cancer Australia systematic review, Appendix L.[9]

Areas for ongoing research for first-line adjuvant treatment of epithelial ovarian cancer include:

- Effective chemotherapy regimen
- Effective schedule for chemotherapy regimens
- Effective mode of administration of chemotherapy

A number of international trials are in progress to further assess the applicability of dose-dense regimens for use in other populations, including the Italian trial MITO7, ICON8 AND GOG 262.

Other international trials that are in progress which are of interest are GINECO and GOG 273.

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APPENDIX 1: NHMRC Evidence Hierarchy

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question[88]

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: • an independent, blinded • comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial(i.e. alternate allocation or some other method)	A study of test accuracy with: • an independent, blinded comparison with a valid reference standard, among non-consecutive persons with • a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
III-2	A comparative study with concurrent controls: • Non-randomised, • experimental trial • Cohort study • Case-control study • Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, • experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm • study • Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

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Additional information

Topic-specific guideline development process

Priority topic areas for guideline development are determined in consultation with key stakeholders including experts in relevant disciplines and consumer representatives. A specific multidisciplinary Working Group, including consumers, is established for each topic identified and is involved in all aspects of guideline development. A systematic evidence review is undertaken for each guideline. All members are asked to declare any conflicts of interest and these declarations are recorded. The content of the guideline is not influenced by any external funding body. The guideline is reviewed externally by key stakeholders and the wider community and endorsement is sought from relevant professional colleges and groups in Australia.

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