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DNA-repair pathway inhibitors for the treatment of ovarian cancer

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Abstract

Background—Ovarian cancer is the sixth most common cancer and seventh most common cause of cancer death in women world-wide.Three-quarters of women present when the disease has spread through-put the abdomen (stage III or IV) and treatment consists of a combination of debulking surgery and platinum-based chemotherapy, with or without taxanes. Although initial responses to chemotherapy are often good, most women will relapse and require further chemotherapy and will eventually develop resistance to chemotherapy agents. Increased understanding about the molecular basis of ovarian cancer has lead to the development of novel agents, which work in different ways to conventional chemotherapy. These include DNA-repair pathway inhibitors, the commonest of which are the PARP (poly (ADP-ribose) polymerase) inhibitors. It is therefore important to compare their effectiveness and side effects of these novel agents to assess their role in the treatment of advanced ovarian cancer, especially as treatment of advanced disease is aiming to improve length of survival and quality of life (QoL).

Objectives—To compare the effectiveness and harmful effects of interventions, which inhibit DNA-repair pathways, in the treatment of ovarian cancer.

Search methods—RCTs were identified by searching The Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2, 2009), The Cochrane Gynaecological Cancer

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CONTRIBUTIONS OF AUTHORS The protocol was written by JM and KG, with significant input from HD and AB. SK and JM had the initial concept for the title. IM and KH analysed the results of the searches and contacted regulatory bodies and pharmaceutical companies for grey literature searches and additional information. IM, KH, and JM wrote the review with significant input from AB. SK and SN approved the final version of the protocol and review.
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DECLARATIONS OF INTEREST None

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Collaborative Review Group's Trial Register, MEDLINE (1990 to June 2009), EMBASE (1990 to June 2009), ongoing trials on www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and the National Research Register (NRR), the FDA database and pharmaceutical industry biomedical literature.

Selection criteria—Adult women with histologically proven ovarian cancer who were randomised to treatment groups which either compared DNA-repair pathway inhibitors with no treatment or DNA-repair pathway inhibitors together with conventional chemotherapy compared with conventional chemotherapy alone.

Data collection and analysis—Two review authors independently assessed whether potentially relevant studies met the inclusion criteria. Searches for additional data and information were also performed by two independent review authors. No trials were found and therefore no data were analysed, so only information on excluded references was collected.

Main results—The search strategy identified 473 unique references of which 461 were excluded on the basis of title and abstract. The remaining 12 articles were retrieved in full, but none satisfied the inclusion criteria. However, two ongoing randomised phase II clinical trials were identified from the clinical trials databases that met our inclusion criteria, but no preliminary data were available.

Authors' conclusions—There are to date no published RCT data on the effectiveness and side effects of DNA-repair pathways inhibitors used alone or in association with conventional chemotherapy in the treatment of ovarian cancer. On-going trials have been identified and results are awaited and will be included in future updates of this review.

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; DNA Repair [*drug effects]; Ovarian Neoplasms [*drug therapy; genetics]; Phthalazines [therapeutic use]; Piperazines [therapeutic use]; Poly(ADP-ribose) Polymerases [*antagonists & inhibitors]

MeSH check words

Adult; Female; Humans

BACKGROUND

Description of the condition

Each year, world-wide, over 200,000 women are diagnosed with ovarian cancer and nearly 125,000 die from the disease, corresponding to an annual incidence of 6.6 cases per 100,000 women, an annual mortality rate of 4.0 deaths per 100,000 and a cumulative lifetime risk of 0.5% (GLOBOCAN 2002). In terms of incidence, it is the sixth most common cancer and it is the seventh most common cause of cancer death in women. The onset is often insidious; the symptoms are vague and may mimic other conditions. This may lead to a delay in diagnosis, and currently three-quarters of women with ovarian cancer are diagnosed when the disease has spread throughout the abdomen (stage III or IV) (Shepherd 1989) when the 5 year survival is 20 to 30% (Jemal 2008). Epithelial ovarian cancer, which arises from the

surface of the ovary, accounts for 90% of all ovarian cancers and typically presents in post-menopausal women, with a peak incidence when women are in their early sixties, although it does occur in younger women, often associated with genetic predispositions (Quinn 2001).

Description of the intervention

Management of advanced ovarian cancer consists of debulking surgery, and platinum-based chemotherapy, with or without the addition of a taxane (Morrison 2007; Stewart 1999) and a recent RCT found that there was no difference in survival, if surgery were performed before or after the first three cycles of chemotherapy (Vergote 2008). However, in women presenting with advanced disease, there has been little change to the five-year survival for stage III to IV disease over the past 20 to 30 years (Engel 2002). Despite good initial responses to platinum agents and taxanes, most women have disease relapse, require further treatment with chemotherapy, and eventually develop resistance to conventional chemotherapeutic agents.

Conventional chemotherapeutic agents have activity on all rapidly dividing cells, hence the common side effects such as: hair loss; bone marrow suppression; and mucositis. Increasing knowledge of the genetic basis for cancer has lead to the development of novel reagents, which target cancer-specific pathways. It is hoped that these reagents will spare normal cells and reduce the toxic side effects of chemotherapy, in addition to having an enhanced therapeutic effect.

How the intervention might work

DNA repair inhibition—Many current therapies for cancer (e.g. cytotoxic chemotherapy and radiotherapy) work by damaging DNA. As this function is fundamental to cell survival there are a number of systems or pathways of DNA repair. Cancer cells are more susceptible to DNA damage than normal cells, because the multiple mutations that have caused cells to become cancerous often affect one or more of these DNA repair pathways.

A number of drugs have been developed, which take advantage of this susceptibility of cancer cells to DNA damage. They work by inhibiting some, but not all, DNA repair pathways. In normal cells other DNA-repair pathways will compensate. However, cancer cells often have mutations in other DNA-repair pathways, and so DNA damage is not repaired, leading to cell death.

Small-molecule agents have been identified which target elements in a number of these pathways, including poly (ADP-ribose) polymerase (PARP), DNA-dependent protein kinase (DNA-PK), and ATM (Bryant 2006). Of these DNA-repair inhibitors, PARP inhibitors have been most commonly used as anti-cancer therapy.

PARP inhibitors—PARPs are a family of related enzymes, which are involved in regulating various cellular processes, including DNA repair, cell death, and inflammation. PARP inhibitors therefore have a potentially wide range of applications (Jagtap 2005).

PARP-1 is the most-studied of the PARP family. It is a nuclear enzyme, which binds to both single-stranded and double-stranded DNA breaks, either facilitating their repair by other

enzymes (in the case of mild damage), or triggering cell-death pathways (in the case of more severe damage) (Curtin 2005; Peralta-Leal 2008; Ratnam 2007).

Research into the anti-cancer applications of PARP inhibitors has focused on two main approaches:

First, they can be used in isolation against certain cancers with significant mutations in their DNA-repair pathways: specifically, those with mutations in the BRCA 1/2 genes (which predispose to inherited forms of breast cancer and some ovarian cancers) (Zaremba 2007). BRCA genes encode for DNA repair enzymes independently of the PARP pathway. Cells with BRCA mutations are very susceptible to PARP inhibitors, because both pathways to repair DNA are blocked and so this triggers cell cycle arrest and apoptosis specifically within cells which have the BRCA mutation (Bryant 2005; Farmer 2005). PARP-1 inhibitors have been shown to be effective when used alone in cell culture or in mouse models at killing cells with mutations in the BRCA1 and BRCA2 genes, (Bryant 2005; Farmer 2005) and have been used in clinical trials for breast cancer (Fong 2008).

Second, PARP inhibitors can be used in combination with conventional anti-cancer agents that act by damaging DNA, such as cytotoxic chemotherapy and radiotherapy, as the PARP-inhibitors block the DNA-repair mechanisms which cancer cells use to resist destruction.

Why it is important to do this review

Novel biological agents that work in different ways to conventional chemotherapy, have been developed. It is therefore important to establish whether the addition of these new drugs to conventional chemotherapy regimens is beneficial, in terms of survival, and if so, at what cost, in terms of additional harmful effects. Furthermore, since these compounds may be less toxic compared to conventional chemotherapy agents, it may be feasible to use these new agents in patients who are not currently taking chemotherapy (so called maintenance treatment), to reduce the chance of, or delay, the recurrence of their ovarian cancer.

OBJECTIVES

To compare the effectiveness and harmful effects of interventions, which inhibit DNA-repair pathways, in the treatment of ovarian cancer.

METHODS

Criteria for considering studies for this review

Types of studies—Randomized controlled trials (RCTs)

Types of participants—Adult women with histologically proven ovarian cancer. Women with other concurrent malignancies were excluded.

Types of interventions—

- DNA-repair pathway inhibitors versus no treatment

- DNA-repair pathway inhibitors + conventional chemotherapy versus conventional chemotherapy

Types of outcome measures

Primary outcomes:

1. Overall survival (OS)

Secondary outcomes:

1. Progression-free survival (PFS)
2. Quality of life (QOL), measured by a validated scale
3. Toxicity: Grades of toxicity were grouped (CTEP 2006) as follows:
    i. haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage)
    ii. gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis)
    iii. genitourinary
    iv. skin (stomatitis, mucositis, alopecia, allergy)
    v. neurological (peripheral and central)
    vi. other side effects not categorised above

Search methods for identification of studies

Papers in all languages were sought and translations were carried out where necessary.

Electronic searches—See: Cochrane Gynaecological Cancer Group methods used in reviews.

The following electronic databases were searched:

- The Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register
- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE
- EMBASE

The MEDLINE, Embase and CENTRAL search strategies, based on terms related to the review topic, are presented in (Appendix 1, Appendix 2 and Appendix 3).

Databases were searched from 1990 until June 2009.

All relevant articles found were identified on PubMed using the 'related articles' feature and further search was carried out for newly published articles.

Searching other resources—Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and the National Research Register (NRR) were searched for ongoing trials. Details of ongoing or unpublished trials were also sought from the Food and Drug Administration (FDA) (www.fda.gov) and the European Medicines Agency (EMEA) (www.emea.europa.eu), and from pharmaceutical company sources. The main investigators of the relevant ongoing trials were contacted for further information, as were the major co-operative trials groups active in this area. Astra Zeneca was identified as the company responsible for ongoing studies and was contacted for preliminary data on these studies. The reference lists of all included trials were searched for further relevant trials.

Data collection and analysis

Selection of studies—All titles and abstracts retrieved by electronic searching were downloaded to the reference management database *Endnote*, duplicates were removed and the remaining references were examined by two review authors (IM, KH) independently. Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers was assessed independently by two review authors (IM, KH). Reasons for exclusion were documented. We did not identify any trials suitable for inclusion in the review. Should such trials be identified for future updates of the review the following methods will be employed (see below).

Data extraction and management—For included studies, data will be abstracted as follows:

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
    - ○ Total number enrolled
    - ○ Patient characteristics
    - ○ Age
    - ○ Co-morbidities
    - ○ Previous treatment
- Total study duration
- Total number of intervention groups
- Ovarian cancer details at diagnosis

- FIGO stage
- Histological cell type
- Tumour grade
- Extent of disease

- Intervention details
  - Type of DNA-repair pathway inhibitor
  - Dose
  - Duration of treatment
  - Consolidation treatment or treatment of active disease
- Comparison details
  - Type of control: conventional chemotherapy or no treatment
  - Dose (if appropriate)
  - Duration (if appropriate)
- Deviations from protocol
- Risk of bias in study (see below)
- Duration of follow-up
- Outcomes: Overall survival, progression-free survival, quality of life (QoL), toxicity;
  - For each outcome: Outcome definition (with diagnostic criteria if relevant);
  - Unit of measurement (if relevant);
  - For scales: upper and lower limits, and whether high or low score is good
  - Results: Number of participants allocated to each intervention group;
  - For each outcome of interest: Sample size; Missing participants.

Data on outcomes will be extracted as below:

- For time to event (overall and progression-free survival) data, we will extract the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these are not reported, we will attempt to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. toxicity or deaths if it was not possible to use a HR), we will extract the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a relative risk (RR).
- For continuous outcomes (e.g. quality of life measures), we will extract the final value and standard deviation of the outcome of interest and the number of patients

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assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.

Both unadjusted and adjusted statistics will be extracted, if reported. When adjusted results are extracted, the variables that were adjusted for will be recorded.

Where possible, all data extracted will be those relevant to an intention-to-treat analysis, in which participants are analysed in groups to which they were assigned.

The time points at which outcomes were collected and reported will be noted.

Data will be abstracted independently by two review authors (IM, KG) onto a data abstraction form specially designed for the review. Differences between review authors will be resolved by discussion or by appeal to a third review author (JM) if necessary.

Assessment of risk of bias in included studies—The risk of bias in included RCTs will be assessed using the Cochrane Collaboration's tool and the criteria specified in Chapter 8 of the Cochrane Handbook (Higgins 2008). This will include assessment of:

- sequence generation
- allocation concealment
- blinding (of participants, healthcare providers and outcome assessors)
- incomplete outcome data:
    - ○ We will code the satisfactory level of loss to follow-up for each outcome as:
        - ◇ Yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
        - ◇ No, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms
        - ◇ Unclear if loss to follow-up was not reported
- selective reporting of outcomes
- other possible sources of bias

The risk of bias tool will be applied independently by two review authors (IM, KH) and differences will be resolved by discussion or by appeal to a third reviewer (JM). Results are summarised in both a risk of bias graph and a risk of bias summary. Results of meta-analyses will be interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect—We will use the following measures of the effect of treatment:

- For time to event data, we will use the HR, if possible.
- For dichotomous outcomes, we will use the RR.

- For continuous outcomes, we will use the mean difference between treatment arms if all trials measured the outcome on the same scale, otherwise standardised mean differences will be used.

Dealing with missing data—We will not impute missing outcome data; if only imputed outcome data were reported, we will contact trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity—Heterogeneity between studies will be assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001).If there was evidence of substantial heterogeneity, the possible reasons for this will be investigated and reported.

Assessment of reporting biases—Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects. When there is evidence of small-study effects, publication bias will be considered as only one of a number of possible explanations. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, sensitivity analyses will be performed using fixed effects models.

Data synthesis—If sufficient, clinically similar trials are available their results will be pooled in meta-analyses. Adjusted summary statistics will be used if available; otherwise unadjusted results will be used.

- For time-to-event data, HRs will be pooled using the generic inverse variance facility of RevMan 5.
- For dichotomous outcomes, the RR will be calculated for each study and these will then be pooled.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences will be pooled.

If any trials have multiple treatment groups, the ‘shared’ comparison group will be divided into the number of treatment groups and comparisons between each treatment group and the split comparison group will be treated as independent comparisons.

Random effects models with inverse variance weighting will be used for all meta-analyses (DerSimonian 1986).

If possible, indirect comparisons using the methods of Bucher 1997 will be used to compare competing interventions that have not been compared directly with each other.

Subgroup analysis and investigation of heterogeneity—As we expect to find few trials, we do not plan any sub-group analyses. However, factors such as type of intervention (e.g. use as early stage consolidation therapy in chemo-sensitive cancers or use in late stage

chemo-resistant cancers) and stage of disease will be considered in interpretation of any heterogeneity.

Sensitivity analysis—Sensitivity analyses will be performed excluding (i) studies at high risk of bias, (ii) unadjusted results.

RESULTS

Description of studies

See: Characteristics of excluded studies; Characteristics of ongoing studies.

See: Characteristics of ongoing studies; Characteristics of excluded studies.

Results of the search—An initial broad search was run and yielded 473 unique articles after deletion of duplicates. The abstracts of these were reviewed independently by two review authors and articles which obviously did not meet the inclusion criteria were excluded at this stage. Twelve articles were retrieved in full and translated into English where appropriate. The full text screening of these 12 studies excluded all 12 trials for the reasons described in the table Characteristics of excluded studies. However, two on-going RCTs (Assessment of AZD2281; ICEBERG 3), were identified from the clinical trials databases that met our inclusion criteria and are described in the table Characteristics of ongoing studies.

Searches of the grey literature did not identify any additional relevant studies.

Included studies—No trials were identified that met our inclusion criteria.

Excluded studies—Twelve references were excluded, after obtaining the full text, for the following reasons:

- Four studies (Fong 2006; Fong 2008; Fong 2009; Yap 2007) were non-randomised single arm phase I non-randomised studies of one PARP inhibitor (AZD2281)
- Seven references (Ashworth 2008; Drew 2008; Helleday 2008; Lord 2008; Muggia 2009; Turner 2005; Yap 2009) were narrative review articles and did not include any study which met our inclusion criteria
- One study (Audeh 2009) was a non-randomised phase II study of AZD2281.

Risk of bias in included studies

No trials were found and therefore the risk of bias tool was not applied.

Effects of interventions

No data were available.

DISCUSSION

Summary of main results

We did not find any evidence to support the use of DNA-repair pathway inhibitors for ovarian cancer outside of on-going clinical trials.

Two randomised phase II studies were found, which met with our inclusion criteria, but are on-going and no preliminary data were available from the investigators. One trial began in August 2008 and is now closed to recruitment. This a phase II randomised, double blind, multicenter study to assess the efficacy of AZD2281 in platinum sensitive serous ovarian cancer patients (Assessment of AZD2281; NCT00753545). This trial is due to finish in June 2011.

The second ongoing trial started recruitment in July 2008 and is a phase II, open-label, randomised, comparative, international multicenter trial. The aim of the trial is to assess the safety and efficacy of different doses of AZD2281 given orally twice daily versus intravenous liposomal doxorubicin given monthly in women with advanced BRCA1- or BRCA2- associated ovarian cancer, who have failed previous platinum-based chemotherapy (ICEBERG 3; NCT00628251). Completion of this trial is due in September 2010.

Overall completeness and applicability of evidence

We searched both published and unpublished databases and sought additional information from the American and European regulatory bodies and from pharmaceutical companies who have developed DNA-repair inhibitors and who have conducted early stage trials with these agents. No completed trials were identified, although two on-going trials were found. It is unlikely that there are any completed trials that we have not identified.

Quality of the evidence

No completed trials were identified that met our inclusion criteria.

Potential biases in the review process

Both published and unpublished trials were sought and databases containing details of on-going studies identified two on-going trials, which are likely to meet our inclusion criteria. Although negative data are less likely to be published, we have had no indication that such trials exist from searching the clinical trials databases and the American and European regulatory bodies, and from our contact with investigators of on-going studies.

Agreements and disagreements with other studies or reviews

No other review article commented on any completed trial which met the inclusion criteria for this review. One of the excluded studies in this review was a phase I human study of AZD 2281 (Fong 2009). This study included 60 patients with a range of solid tumours that were refractory to standard therapies. Among these patients, 35% had ovarian cancer. AZD2281 had few of the adverse effects of conventional chemotherapy and showed anti-tumour activity in cancer associated with BRCA1 or BRCA2 mutation.

AUTHORS' CONCLUSIONS

Implications for practice

There are as yet no data to recommend PARP inhibitors alone or in association with conventional chemotherapy as standard treatment, in women with ovarian cancer. The use of DNA-repair pathway inhibitors as treatment for ovarian cancer is currently indicated only for women as part of on-going trials.

Implications for research

There are currently two RCTs on-going which are investigating the role of DNA-repair inhibitors in the treatment of ovarian cancer. One trial is assessing the efficacy of AZD2281 in platinum sensitive serous ovarian cancer patients (Assessment of AZD2281). The second trial is assessing the safety and efficacy of different doses of AZD2281 compared to liposomal doxorubicin in patients with advanced BRCA1- or BRCA2- associated ovarian cancer after failed platinum-based chemotherapy (ICEBERG 3). Results of these trials are eagerly awaited and it is likely that other DNA-repair pathway inhibitors, currently at earlier stages of development, will be available for randomised clinical trials in the near future.

Acknowledgments

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SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR CCRCD, UK.

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- Macmillan Cancer Supoort, UK.

JM is a subspecialist trainee in gynaecological oncology. This 50% clinical post is funded by a grant from Macmillan Cancer Support.

- Department of Health, UK.

NHS Cochrane Collaboration programme Grant Scheme CPG-506

Appendix 1. MEDLINE search stragegy

Medline Ovid 1950 to June week 3 2009

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.

5. drug therapy.fs.
6. randomly.ab.
7. rial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. (animals not (humans and animals)).sh.
11. 9 not 10
12. ovar*.mp.
13. (cancer* or carcinoma*or neoplasm* or tumor*or tumour*or malignan*).mp.
14. 12 and 13
15. exp Ovarian Neoplasms/
16. 14 or 15
17. exp DNA Repair Enzymes/
18. exp DNA Repair/
19. DNA repair.mp.
20. exp “Poly(ADP-ribose) Polymerases”/
21. (PARP adj5 inhibit*).mp.
22. (poly ADP ribose polymerase adj5 inhibit*).mp.
23. (olaparib or AZD2281 or KU59436).mp.
24. AG014699.mp.
25. ABT-888.mp.
26. BSI-201.mp.
27. INO-1001.mp.
28. MK4827.mp.
29. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 11 and 16 and 29

key:

pt=publication type

ab=abstract

fs=floating subheading

mp=title, original title, abstract, name of substance word, subject heading word

sh=subject heading

Appendix 2. EMBASE search strategy

Embase Ovid 1980 to 2009 week 25

1. exp Controlled Clinical Trial/
2. randomized.ab.
3. placebo.ab.
4. dt.fs.
5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animal not (human and animal)).sh.
10. 8 not 9
11. (ovar* and (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan*)).mp.
12. exp Ovary Tumor/
13. 11 or 12
14. exp Polydeoxyribonucleotide Synthase/
15. exp DNA Repair/
16. DNA repair.mp.
17. exp Nicotinamide Adenine Dinucleotide Adenosine Diphosphate Ribosyltransferase/
18. (PARP adj5 inhibit*).mp.
19. (poly ADP ribose polymerase adj5 inhibit*).mp.
20. (olaparib or AZD2281 or KU59436).mp.
21. AG014699.mp.
22. ABT-888.mp.
23. BSI-201.mp.
24. INO-1001.mp.
25. MK4827.mp.
26. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 10 and 13 and 26

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key:

ab=abstract

fs=floating subheading

sh=subject heading

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

Appendix 3. CENTRAL search strategy

CENTRAL Issue 2 2009

#1 ovar* and (cancer* or carcinom* or neoplasm* or tumor* or tumour* or malignan*)

#2 MeSH descriptor Ovarian Neoplasms explode all trees

#3 (#1 OR #2)

#4 MeSH descriptor DNA Repair Enzymes explode all trees

#5 MeSH descriptor DNA Repair explode all trees

#6 DNA repair

#7 MeSH descriptor Poly(ADP-ribose) Polymerases explode all trees

#8 PARP near/5 inhibit*

#9 poly ADP ribose polymerase near/5 inhibit*

#10 olaparib or AZD2281 or KU59436

#11 AG014699

#12 ABT-888

#13 BSI-201

#14 INO-1001

#15 MK4827

#16 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)

#17 (#3 AND #16)

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 6, 2010

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ashworth 2008	Review article
Audeh 2009	Phase II single arm trial of the oral PARP inhibitor olaparib (AZD2281) in BRCA-deficient advanced ovarian cancer (ASCO 2009 meeting abstract)
Drew 2008	Review article
Fong 2006	Phase I pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of a small molecule inhibitor of Poly ADP-Ribose Polymerase (PARP), KU-0059436 (Ku) in patients with advanced tumours (ASCO 2006 meeting abstract)
Fong 2008	Results from a phase I study of AZD2281 (KU-0059436), a PARP (poly ADP-ribose polymerase) inhibitor with single agent anticancer activity in patients with BRCA deficient ovarian cancer (ASCO 2008 meeting abstract)
Fong 2009	Non-randomised phase I clinical trial analysing the pharmacokinetic and pharmacodynamic characteristics of olaparib (AZD2281). Selection was aimed at having a study population enriched in carriers of a BRCA1 or BRCA2 mutation
Helleday 2008	Review article
Lord 2008	Review article
Muggia 2009	Review article
Turner 2005	Review article
Yap 2007	Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of KU-0059436 (Ku), a small molecule inhibitor of poly ADP-ribose polymerase (PARP) in cancer patients, including BRCA1/2 mutation carriers (ASCO 2007 meeting abstract)
Yap 2009	Review article

Characteristics of ongoing studies *[ordered by study ID]*

Assessment of AZD2281

Trial name or title	Assessment of Efficacy of AZD2281 in Platinum Sensitive Serous Ovarian Cancer
Methods	Phase II Randomised, Double Blind, Multicenter Study
Participants	Women with platinum-sensitive serous ovarian tumours following treatment with two or more platinum-containing regimens
Interventions	Randomisation to AZD2281 or placebo
Outcomes	**Primary:** • Efficacity measured by Progression-free survival (PFS) **Secondary:** • Overall survival (OS) • Best overall response (ORR) • Duration of response • Cancer antigen (CA)-125 response measured every 28 days • Radiological tumour assessments will be performed every 12 weeks for 1st 60 weeks and then every 24 weeks

Trial name or title	Assessment of Efficacy of AZD2281 in Platinum Sensitive Serous Ovarian Cancer
	• Safety assessments every 28 days: adverse events (AEs), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry, haematology and urinalysis.
Starting date	August 2008
Contact information	Information.Center@astrazeneca.com
Notes	http://clinicaltrials.gov/show/NCT00753545

ICEBERG 3

Trial name or title	Dose-finding Study Comparing Efficacy and Safety of a PARP Inhibitor Against Liposomal Doxorubicin in BRCA positive Advanced Ovarian Cancer (ICEBERG 3)
Methods	Phase II, Randomised,Open-Label, Comparative, International Multicenter Study
Participants	• Advanced ovarian cancer with positive BRCA1 or BRCA2 status • Progressive or recurrent disease after platinum-based chemotherapy
Interventions	**Experimental arm:** AZD2281 given at 400 mg twice daily AZD2281 given at 200 mg twice daily **Active comparator arm:** Liposomal Doxorubicin (LPD) 50mg/m^2 intravenously every 4 weeks
Outcomes	**Primary** • Efficacity measured by Progression-free survival (PFS) • Best overall response (ORR) • Duration of response • Cancer antigen (CA)-125 response measured every 4 weeks • Radiological tumour assessments will be performed every 12 weeks for 1st 60 weeks and then every 24 weeks **Secondary** • Comparison of safety and tolerability
Starting date	July 2008
Contact information	Information.Center@astrazeneca.com
Notes	http://clinicaltrials.gov/show/NCT00628251

DATA AND ANALYSES

This review has no analyses.

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

Are DNA repair inhibitors as effective and harmless compared to conventional chemotherapy in the treatment of ovarian cancer?

Ovarian cancer is the sixth commonest cancer in women world-wide and remains a leading cause of death, with an annual incidence of 6.6 cases per 100,000 women and an annual mortality rate of 4.0 deaths per 100,000 women. Most ovarian cancers (90%) are epithelial ovarian cancer and arise from the surface of the ovary. Epithelial ovarian cancer typically occurs in post-menopausal women, with a peak incidence around the age of 60, although it does occur in younger women, often associated with genetic predispositions. The onset of this disease is insidious and 75% of women present with advanced stage disease (stage III or IV) when the 5 year survival is around 30%. Treatment consists of debulking surgery and platinum-based chemotherapy, with or without taxanes. Although initial response to chemotherapy is good, most women will relapse, requiring further chemotherapy treatment and develop cancer that is resistant to chemotherapy.

Conventinal chemotherapy acts on all rapidly dividing cells by damaging DNA. Cancer cells divide very rapidly, which is why chemotherapy works better on cancer cells than normal cells. However, there is no inherent selectivity for normal calls and so rapidly dividing cells, such as gut lining, hair follicles and bone marrow, are also affected, leading to diarrhoea, mouth ulcers, hair loss, anaemia and susceptibility to infections.

All cells are equipped with a number of systems or pathways that repair DNA damage. If cells are unable to repair their DNA, the cell undergoes programmed cell death (apoptosis) in order to prevent an abnormal cell from dividing. Because being able to repair DNA is vital to cell survival, normal cells have more than one DNA-repair pathway, so that if one is lost cells can still repair themselves. Cancer cells often develop defects in these pathways, due to mutations, which may promote development of cancer (e.g. BRCA mutations). However, these same mutations mean that these cancer cells are more susceptible to DNA damage, such as that caused by chemotherapy, than normal cells. Novel therapeutical agents have been developed to inhibit DNA-repair pathways, which makes cells that already have faults in another DNA repair pathway due to a mutation, exquisitely sensitive to DNA damaging chemotherapy agents. The most common target for this type of novel anti-cancer agent are the DNA-repair enzymes called poly (ADP-ribose) polymerases (PARPs). PARPs are a family of related enzymes, which are involved in regulating various cellular processes, including DNA repair, cell death, and inflammation. PARP inhibitors therefore have a potentially wide range of applications.

Our objective was to compare effectiveness and side effects of PARP inhibitors compared to conventional chemotherapy in women with ovarian cancer. The identification of a safe dose of AZD2281 (a PARP inhibitor) has been found by small non randomised trials, with encouraging results. For ovarian cancer, there are currently two ongoing RCTs, but outcome data are not yet available. Results of these trials are

awaited to determine if DNA repair inhibitors have a role in addition to conventional chemotherapy in the treatment of ovarian cancer.

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