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Health Technology Appraisal

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer (including review of technology appraisal no. 91 and technology appraisal no. 222) [ID 468]

About you

Your name: [redacted]

Name of your organisation: NCRI/RCP/RCR/ACP/JCCO

Comments coordinated by: [redacted]

What is the expected place of the technology in current practice?

Management of recurrent ovarian cancer

Before discussing the technologies in detail, it is important to emphasise that there have been very considerable improvements in our understanding of the biology of ovarian cancer since TA91, the last comprehensive appraisal of treatment of recurrent ovarian cancer. The most noticeable alteration is the realisation that the five major subtypes of ovarian cancer (high grade serous, low grade serous, clear cell, endometrioid and mucinous) are essentially five different diseases, linked only by a common anatomical location. Indeed, many 'ovarian' cancers arise from non-ovarian tissues – high grade serous carcinomas appear to arise from the distal fallopian tube; a large proportion of both clear cell and endometrioid carcinomas develop on a background of endometriosis (ie from ectopic endometrial tissue); nearly mucinous ovarian tumours are actually metastases from non-ovarian primary tumours, including the gastrointestinal tract. The exact cell of origin of low-grade serous tumours remains unclear, although many develop within serous borderline (low malignant potential) tumours. The previous assertion that ovarian cancers arise within ovarian surface epithelial cells is now considered largely incorrect. These findings were revealed by pathological and genomic studies, which indicate that the subtypes have distinct and, with the exception of clear cell and endometrioid cancers, non-overlapping molecular anomalies. The best-defined type is high grade serous, where mutations in p53 are almost universal and approximately 50% have defects in the homologous recombination pathway of DNA damage repair.

It is important to recognise this molecular revolution because the clinical management lags some distance behind: ovarian cancer is largely still treated as though it were a single disease entity. High grade serous cancer is the commonest subtype (at least 60 - 70% of all ovarian cancers) and nearly all data on chemotherapy responsiveness and survival derive from trials in which most patients have this disease type. However, subtype-specific trials in low grade serous and clear cell carcinomas (as well as specific high grade serous studies) are either under way or in development and the future treatment of ovarian cancer will definitely be determined by subtype.

Despite this, patients with recurrent ovarian cancer are still largely classified according to the time between the completion of their last platinum-containing chemotherapy and current relapse. Any

patient who progresses through platinum-chemotherapy is classified as 'platinum-refractory'; those who relapse within 6 months of their last platinum-containing treatment are classified as 'platinum-resistant', whilst those who progress after more than 6 months are deemed to be 'platinum-sensitive'. As stated within the final scope document, it is important to understand that the terms 'resistant' and 'sensitive' are far from absolute and simply reflect the probability of response to further platinum-containing chemotherapy – this probability ranges from 0% in truly refractory tumours to more than 50% for those (high grade serous) tumours relapsing beyond 12 months.

It is also important to note that these terms are used at all relapses, not just the first: thus a tumour may relapse several times in the 'platinum-sensitive' timeframe before relapsing as 'platinum-resistant'. Similarly, 'platinum-resistance' occurring after first-line therapy may be very different from 'platinum-resistance' occurring after several lines of treatment. Patients in the latter group may have tumours with residual chemosensitivity to drugs, including re-treatment with drugs (both platinum and non-platinum) that they have previously received.

<u>Platinum-sensitive ovarian cancer</u>
Unless platinum allergy intervenes, the universal management of high grade serous ovarian cancer relapsing in the platinum-sensitive timeframe involves platinum-containing chemotherapy. Evidence for platinum responsiveness in non-high grade serous tumours will be discussed later.

Two large trials have suggested that combination chemotherapy has survival advantages over single agent carboplatin. The joint AGO-OVAR/NCIC/EORTC trial [1], published since TA91, randomised 356 women relapsing 6 months or more after first line platinum-based chemotherapy to receive single agent carboplatin (AUC 5) on day 1 or carboplatin (AUC 4 on day 1) plus gemcitabine (1000 mg/m^2 on days 1 and 8): treatment was repeated every 21 days for up to 10 cycles. Results indicated that combination treatment produced greater progression-free survival (PFS) (8.6 vs 5.8 months; HR = 0.72, 95% CI 0.58 – 0.90, p = 0.0031), but did not improve overall survival (OS) (HR = 0.96, 95% CI 0.75 – 1.23, p = 0.735). There was significantly greater haematological toxicity in the combination arm.

ICON4 [2], published prior to TA91, randomised 802 women relapsing 6 months or more after first-line treatment to single agent carboplatin (AUC 5) or carboplatin (AUC 5) and paclitaxel (175 mg/m^2) every three weeks. Both PFS (HR = 0.76, 95% CI 0.66-0.89, p = 0.0004) and OS (HR = 0.82, 95% CI 0.69-0.97, p = 0.02) favoured the combination arm.

Most recently, the CALYPSO trial [3] investigated the combination of carboplatin (AUC 5) and pegylated liposomal doxorubicin (PLD) (30 mg/m^2) every 28 days (CD) compared to carboplatin (AUC 5) and paclitaxel (175 mg/m^2) every 21 days (CP) in women relapsing 6 months or more after first or second line platinum-based therapy, at least one of which must have contained a taxane. The trial was designed as a non-inferiority study and randomised 976 patients. Median PFS was greater for CD than CP (11.3 vs 9.4 months, HR = 0.82, 95% CI 0.72 – 0.94, p = 0.005). Mature OS data have not yet been published in a peer-reviewed journal: however, at ASCO 2011, it was reported that there was no significant difference in OS but that there was a significant imbalance in the crossover rate between PLD and paclitaxel.

Other data from CALYPSO have indicated that CD is associated with fewer toxicities [4] and a significantly lower rate of platinum hypersensitivity [5] than CP. Furthermore, in a pre-planned subgroup analysis, CD was found to be particularly effect in those relapsing 6 – 12 months after last platinum (HR for PFS 0.73 (95% CI 0.58-0.90; p = 0.004 for superiority) [6].

Therefore, the combination regimes of carboplatin/gemcitabine and carboplatin/PLD as well as carboplatin/paclitaxel are widely used in platinum-sensitive relapsed ovarian cancer. Furthermore, women may receive all three regimes – with carboplatin/paclitaxel at time of diagnosis and the other regimes at first and second relapse. The worldwide shortage of PLD for the past 18 months has inevitably increased the amount of carboplatin/gemcitabine prescribed: now that PLD is available again, it is likely that this will alter. There have been no direct comparisons of carboplatin/gemcitabine and CD. Single agent carboplatin is usually only used if patients have significant pre-existing paclitaxel neuropathy or cannot tolerate combination regimes. A recent meta-analysis comparing five randomised trials of combination therapies with single agent platinum confirmed that there was a reduction in death (HR, 0.80; 95% CI, 0.64 to 1.00; p = .050) and a significant improvement in PFS (HR = 0.68; 95% CI, 0.57 to 0.81; $p < .00001$) in favour of combination therapy, based on 865 deaths and 1,167 events (ESMO Raja et al 2012)

Trabectedin

This drug was evaluated by NICE in TA222 in April 2011 on the basis of the OVA-301 trial, which compared single agent PLD (50 mg/m^2 every 28 days) with PLD (30 mg/m^2) plus trabectedin 1.1 mg/m^2 every 21 days) in relapsed ovarian cancer, both platinum-sensitive and platinum-resistant [7].

The mature OS data from the whole trial have been published [7] indicating that the combination did not meet the prespecified OS criteria for success (HR = 0.86, 95% CI 0.72-1.02; p=0.0835). However, an exploratory subgroup analysis suggested that patients in the partially platinum-sensitive subgroup (those relapsing 6 – 12 months following last platinum) treated with PLD and trabectedin had greater PFS (7.4 vs 5.5 months) and OS (23 vs 17.1 months, HR = 0.59; 95% CI 0.43-0.82, p = 0.0015) than those treated with PLD alone [8].

The forthcoming INOVATYON trial will directly compare PLD and trabectedin with carboplatin/PLD in the population relapsing at 6 – 12 months.

Platinum-resistant ovarian cancer

Most of the data on single agent topotecan, PLD and gemcitabine in platinum-resistant disease considered in TA91 remain valid in 2013.

Single agent gemcitabine is rarely used, although data from 2007 indicate that, in 195 women with platinum-resistant ovarian cancer, gemcitabine (1000 mg/m^2 days 1 and 8 every 21 days) was equivalent to PLD (50 mg/m^2 every 28 days): response rate 6.1 vs 8.3%; median PFS 3.6 vs 3.1 months; median OS 12.7 vs 13.5 months – all analyses non-significant [9].

For topotecan, one randomised phase II trial has compared weekly administration (4mg/m^2 days 1, 8, 15 every 21 days) with conventional treatment (1.25 mg/m^2 days 1 – 5 inclusive, every 21 days) in 195 women with platinum-resistant disease. Although there was a trend to worsened PFS in the weekly cohort (HR = 1.29, 95% CI, 0.96 to 1.76), OS was the same (HR = 1.04 95% CI, 0.74 to 1.45) and the weekly regime induced significantly less myelosuppression (anaemia, neutropaenia and thrombocytopaenia) [10].

As stated above, ‘platinum resistance’ is a relative term and patients may respond to re-treatment with platinum even if relapse occurs within 6 months of prior platinum therapy. This is best

illustrated by a phase II trial of weekly cisplatin and etoposide in which 46 % patients with platinum-refractory disease (progressing within 4 months of first line therapy) responded [11].

The major change in practice since TA91 has been the use of weekly paclitaxel in platinum-resistant ovarian cancer. Three single arm studies have been published. In 2006, Markman demonstrated a 21% response rate in 48 women with platinum-resistant disease treated with paclitaxel (80mg/m^2 weekly continuously for at least 12 weeks) although PFS and OS data were not reported [12]. Le et al treated 34 platinum-resistant patients with continuous weekly paclitaxel (80 mg/m^2) for up to 24 weeks – in the 32 evaluable patients, the response rate was 54%, whilst PFS and OS for the whole cohort were 6.1 and 10.4 months respectively [13]. A retrospective audit of 53 patients treated at the Royal Marsden Hospital suggested a radiological response rate of 48%, although this cohort included patients with a platinum-free interval of >6 months [14].

There have been no studies directly comparing single agent weekly paclitaxel with either single agent PLD or topotecan. However, weekly paclitaxel has been used as the comparator in randomised studies and retrospective comparisons. In 29 patients treated at a single institution, the response rate to weekly paclitaxel (60 – 70 mg/m^2 given every week) was 48%, with median PFS of 6.2 months [15]. In a randomised phase II comparison of weekly paclitaxel (80 mg/m^2 days 1, 8 and 15, every 28 days) plus placebo with weekly paclitaxel plus two different doses of AMG 386, a peptide-Fc fusion protein that neutralises the interaction between the Tie2 receptor and angiopoietin-1/2, in 161 women with platinum-resistant disease, the objective response rate to weekly paclitaxel plus placebo was 27%, with median PFS 4.6 months and OS 20.9 months [16]. Finally, the CARTHAXY randomised phase II trial compared single agent weekly paclitaxel (80 mg/m^2 days 1, 8 and 15, every 28 days), with the same regime plus carboplatin (AUC 5 d1) or topotecan (3 mg/m^2 days 1, 8 and 15, every 28 days) in 165 women. There was no significant difference in any parameter measured (response rate, PFS or OS), with figures of 20%, 3.7 months and 19.9 months respectively for the control arm [17].

Several randomised phase II studies with weekly paclitaxel as control arm have either recently completed recruitment or are open to recruitment, ensuring that further robust data on the activity of weekly paclitaxel will emerge shortly.

One trial, AURELIA, has allowed patients to receive weekly paclitaxel or PLD or topotecan within the same protocol. In this study, unpublished but presented at ASCO 2012, 361 women with platinum-resistant disease were randomised to chemotherapy with or without concomitant bevacizumab during chemotherapy and as maintenance until progression. Three chemotherapy regimes were allowed at investigators' pre-specified discretion: weekly paclitaxel (80 mg/m^2 days 1, 8 and 15, every 28 days), topotecan (either 4 mg/m^2 days 1, 8,15 or 1.25 mg/m^2 days 1–5 every 21 days) or PLD (50 mg/m^2 every 28 days) and the numbers receiving these regimes in the control groups were similar (55, 63 and 64 respectively). This trial was NOT a randomised comparison between the three control groups – however, the results are illustrative: median PFS for weekly paclitaxel was 3.9 months (95% CI 3.5 – 5.6), for PLD 3.5 months (95% CI 1.9 – 3.9 months) and for topotecan 2.1 months (95% CI 1.9- 3.3 months).

Thus, weekly paclitaxel, usually given on days 1, 8 and 15, repeating every 28 days, has now become a standard-of-care for platinum-resistant ovarian cancer in the UK. This is particularly true in the temporary absence of PLD between 2011 and 2013. However, PLD's main use is likely to be in platinum-sensitive relapse (with carboplatin) rather than as a single agent treatment in

platinum-resistant disease. Thus, weekly paclitaxel is likely to remain the standard-of-care in these patients even with PLD available.

In terms of toxicity, weekly paclitaxel is usually well tolerated. The two most common toxicities are neutropaenia and neuropathy. In the original Markman series, 25% of patients experienced grade 2 – 3 neuropathy: in the more recent randomised studies, the rates are similar (31% all grade neuropathy in AMG386 control arm, 32% grade 2 – 4 neuropathy in CATHAXY control arm). For neutropaenia, rates of grade 3 – 4 toxicity range from 4% to 13%.

One confounding variable is the potential use of weekly paclitaxel-containing regimes as first line therapy in ovarian cancer. The JGOG3016 trial compared standard three-weekly carboplatin and paclitaxel (AUC5 and 175 mg/m^2 both on day 1) with three-weekly carboplatin (AUC5 on day 1) and dose-dense weekly paclitaxel (80 mg/m^2 on days 1, 8 and 15) [18]. Both PFS and OS were significantly improved in the dose-dense weekly paclitaxel arm in 2009: updated, mature PFS and OS data were presented at ASCO 2012 and indicated that the PFS and OS advantages were maintained at a median of 6.4 years of follow up. The ICON8 trial is evaluating the same dose-dense weekly paclitaxel regime in European patients (and also evaluating a regime of weekly carboplatin and weekly paclitaxel) – if it confirms the advantage seen in JGOG3016, weekly paclitaxel regimes will almost certainly become a standard-of-care in the first line setting: it is unclear, however, whether patients will continue to benefit from single agent weekly paclitaxel in the relapsed, platinum-resistant setting.

There have been several small, non-randomised studies investigating the use of regimes containing both weekly platinum and weekly paclitaxel in platinum-resistant disease published before and since TA91. Havrilesky et al investigated carboplatin (AUC2) and paclitaxel (80 mg/m^2) both given on days 1, 8, 15 of a 28 day cycle. They reported that 3/8 patients with platinum-resistant disease responded [19]. The so-called 'Leuven' regime (carboplatin AUC 4, paclitaxel 90 mg/m^2 given on days 1 and 8 of a 3 week cycle) was evaluated in 33 women with recurrent disease of whom only 9 were platinum-resistant. 3 of the 8 evaluable platinum-resistant patients responded with a median PFS of 6.8 months and median OS of 8 months [20]. In the UK, the Imperial College team reported on 20 patients treated with carboplatin (AUC3) and paclitaxel (70 mg/m^2) both given on days 1, 8, 15 of a 28 day cycle. Their response rate was 60% (radiological), and median PFS 7.9 months. OS was only 13.3 months, however [21]. Overall, given their small size and the absence of randomisation, it is not possible to say from any of these studies whether the addition of weekly carboplatin genuinely improves response rate or survival compared to weekly paclitaxel alone in platinum-resistant relapse.

From the above, it can be seen that taxanes, whether in first-line care or as part of treatment for recurrent disease, are key drugs for ovarian cancer. Allergy to paclitaxel is uncommon (and usually occurs early in its use) but is significant when it occurs. Denying patients access to this drug disadvantages them. In this unusual circumstance, albumin-bound paclitaxel, which is not licensed for ovarian cancer (no commercial incentive) can be used safely [22].

<u>Low-grade serous and clear cell carcinomas</u>

As stated above, the large majority of patients in all ovarian cancer trials have had high-grade serous disease. Moreover, prospective data on response and survival for individual subtypes are not presented in any of the randomised trials. Although there have been no subtype-specific trials in relapsed ovarian cancer, retrospective data in both low-grade serous and clear cell carcinomas indicate that the delineators of 'platinum-sensitive' and 'platinum-resistant' are largely irrelevant in

these diseases because response rates to platinum are universally low and also that conventional chemotherapy regardless of type has very little impact in terms of response.

A retrospective analysis of 58 women with true low-grade serous ovarian cancer treated at the MD Anderson Cancer Center in Texas indicated that the response rate to platinum chemotherapy in 'platinum-sensitive' relapse was 4.9% whilst the response rate to any chemotherapy in 'platinum-resistant' relapse was only 2.1%. There was no significant difference in time to progression between these two groups but, in keeping with the indolent nature of low-grade serous tumour growth, median OS was 87 months for the whole cohort [23]. The authors' conclusion is that recurrent low grade serous ovarian cancers are essentially chemotherapy resistant and that other treatments are desperately required. In a recent phase II trial with single agent selumetinib, a MEK inhibitor, 15% patients responded and 65% had stable disease [24]. Consequently, two separate phase III trials comparing MEK inhibition with standard chemotherapy (to include PLD, topotecan and weekly paclitaxel) are about to launch in the UK and USA – these will provide invaluable data on true response rates to conventional therapy in low grade serous tumours. One of the trials, LOGS, will also allow hormonal therapy as one of the control arms given the high rate of ER and PR expression in these tumours.

The only data on chemotherapy in relapsed clear cell carcinoma are also retrospective. Using strict criteria for analysis, researchers at six Japanese institutions identified 75 women who had relapsed following initial surgery and chemotherapy, which was platinum-based in 67 cases. In the 24 patients who relapsed more than 6 months following first-line therapy, the response rate to platinum chemotherapy was 8% (2/24). For those relapsing at less than 6 months, the response rate was 6% (3/51). These data suggest that relapsed clear cell carcinoma, much like low-grade serous, is very resistant to conventional chemotherapy. However, unlike low-grade serous, the clinical course of relapsed clear cell carcinoma is less indolent – the median OS was 16 and 7 months respectively for the >6 month and <6 month cohorts [25]. A European randomised phase II trial in relapsed 'platinum-resistant' clear cell carcinoma of the ovary is due to launch later in 2013 – patients will be randomised between conventional chemotherapy (to include PLD, topotecan and weekly paclitaxel) and the oral triple angiokinase inhibitor BIBF1120 (nintedanib).

In summary, we argue that ovarian cancer is not one disease, but a collection of tumours with different clinical behaviour. As a consequence, some patients have rapidly progressive disease that is difficult to control with one line of treatment following recurrence and that others may live for many years, receiving multiple lines of treatment before irreversible drug resistance eventually appears. During this time, decisions about treatment choices are based on broad categorisation of 'platinum-sensitivity' and discussion of side-effects and benefits with patients. Thus, the selection of therapies is based on a list of a number of options that should be available. The order of selection may vary following discussion between patients and physicians.

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

One of the key issues to highlight from our review above is the great variability in disease behaviour. There is growing recognition that ovarian cancer is not one disease, and that many patients benefit from a number of different courses of treatment. Whilst the cure rate has changed

little over the last two decades, there has been a significant increase the 5 year survival (33 to 44% [NCIN 2012]), largely due to the more effective use of multiple drugs. The recognition of the complexity of this relatively uncommon cancer couple with evidence of improved survival in large centres by surgical and oncological specialists has led to centralisation of care with the current cancer networks. There are still variations in survival in different geographic areas (NCIN) but the reasons for this are not clear and are being investigated.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

See above.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Treatment is either given by oncologists specialising in Gynaecological cancers either within centres or in cancer units according to agreed Network Guidelines

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur? Many of the drugs used in ovarian cancer have been available for many years, and some, such as etoposide, are not licensed for use in ovarian cancer. Furthermore, the clinical community has undertaken clinical trials- often large-scale international that have either modified usage, eg weekly as opposed to three weekly paclitaxel, or combining two active agents eg Carboplatin/ PLD (see CALYPSO trial). These two examples fall outwith pharmaceutical company licensing policies, either because there is no commercial gain to take this forward, or the drugs are generic.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The international community has prepared and regularly updates guidelines which are widely available these include the Gynaecologic Cancer Inter Group (4th Ovarian Cancer Consensus meeting, Vancouver 2010) and ESMO Clinical Guidelines (Ann Oncology 2010). These guidelines are prepared following peer discussion and review and are based on published data.

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