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Single Technology Appraisal (STA)

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) [ID468]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Professor Charlie Gourley

Name of your organisation: University of Edinburgh Cancer Research Centre,
Western General Hospital,
Edinburgh

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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

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?

The mainstay of treatment for recurrent ovarian cancer in the NHS is systemic chemotherapy. A small percentage of patients may undergo debulking surgery prior to receiving chemotherapy.
The choice of chemotherapy is highly dependent upon the previous platinum-free interval following previous platinum-based treatment. If disease relapses within 6 months of previous platinum-based chemotherapy (or if the patient's disease progresses on platinum therapy) then that patient's cancer is classified as platinum-resistant. Disease that relapses within 12 months and greater than 12 months after previous platinum therapy is defined as partially platinum sensitive and platinum sensitive respectively.
Most patients with platinum sensitive or partially platinum-sensitive relapsed ovarian cancer currently receive combination platinum-based chemotherapy. This generally means carboplatin and paclitaxel chemotherapy (as per the ICON4 study)[1] although recent data suggest that carboplatin and pegylated liposomal doxorubicin hydrochloride (PLDH) provides a superior progression free survival (PFS) and toxicity profile.[2] The access to this alternative regime varies across the United Kingdom with access straightforward in some areas and only possible through individual patient requests in others. An alternative regime would be carboplatin and gemcitabine, although this is used less often in this setting. In patients who are not fit enough for combination chemotherapy or who have persistent toxicities from previous lines of therapy, single agent carboplatin is a suitable regimen. Single agent cisplatin may be used instead of carboplatin in patients with carboplatin hypersensitivity or if other patient-specific factors suggest that carboplatin may be less well tolerated.
Patients with platinum-resistant ovarian cancer are generally treated with PLDH or weekly paclitaxel (the latter sometimes in combination with weekly carboplatin). The use of topotecan is declining because recent randomised data (AURELIA study; published in abstract form only to date) suggests that the response rate to this single agent in platinum resistant ovarian cancer is extremely low and there is an argument that it should no longer be recommended in this disease. A recent study suggested that the combination of carboplatin AUC4 and gemcitabine 1000mg/m2 on day1 and day8 may be a very useful regime in the platinum resistant setting,[3] with the combination apparently helping to overcome platinum resistance in a significant percentage of patients.

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?

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Ovarian cancer patients with germline BRCA1 and BRCA2 mutations have a superior prognosis to non-germline BRCA mutation carriers (with BRCA2 mutation carriers having a better prognosis than BRCA1 mutation carriers).[4]
In addition there is evidence that patients carrying germline BRCA1 or BRCA2 mutations have a greater chance of responding to PLDH than non germline BRCA1/2 mutation carriers.[5] *Although this trial was not designed to specifically address the question of PLDH sensitivity in BRCA mutation carriers versus non-BRCA mutation carriers the difference in response rate compared to comparable unselected patients in other studies strongly suggests that these patients have greater PLDH sensitivity. The effect of BRCA1/2 mutation status on sensitivity to the other agents being assessed is not known.*

In addition, it is now very clear that ovarian cancer should not be considered as a single disease entity. The 5 main immunohistochemical subtypes (high grade serous, low grade serous, endometrioid, clear cell and mucinous) differ in terms of their stages of presentation, prognosis, chemosensitivity, tissue of origin and underlying molecular genetics. The most important aspect of this with respect to treatment in the relapsed disease setting is that some subtypes are not chemosensitive. The best example is low grade serous ovarian cancer whose response rate to chemotherapy per se is only 4.9% in the platinum-sensitive disease setting and in the platinum-resistant disease setting it is only 2.1%.[6] *As this is a recently recognised disease entity the response rate to the different agents that are part of this assessment is unknown. Similarly, the response rates to the different cytotoxic agents in endometrioid, clear cell and mucinous ovarian cancer has not been clearly established. As 70-80% of relapsed ovarian cancer is high grade serous, much of the available data is most readily applied to this immunohistochemical subtype.*

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)?

Specialist oncology clinics. The specialist nursing required should already exist in these clinics.

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?

These drugs are already available but as stated above there is considerable geographical and between clinician variation with respect to usage. Although these agents are licensed for ovarian cancer, alterations to the recommended scheduling are made (e.g. the use of paclitaxel weekly or the combination of PLDH with carboplatin). These are outside of the license but there is significant evidence to suggest that these regimes are effective.

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.

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The main guidelines that I am aware of are the ESMO (European Society of Medical Oncology) Guidelines and the SIGN (Scottish Intercollegiate Guideline Network). Revision of the latter guidelines for ovarian cancer is almost complete. The methodology used for these is critical appraisal of the literature (after creating an evidence hierarchy) followed by rigorous peer review.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The only alternatives are biological agents which are not approved by NICE, SMC or AWMSG but which can be obtained in England through the Cancer Drugs Fund.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

N/A

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

In this setting the most important clinical trials outcomes are overall survival, progression free survival, toxicity and quality of life. All of these have been taken into account in the clinical trials used to assess these technologies.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

In these patients likely toxicity of the chosen regimen plays a crucial role in deciding which regime is most suitable for a particular patient. Pre-existing toxicities from previous lines of chemotherapy must be considered. A good example is neuropathy. If a patient has significant peripheral neuropathy from preceding chemotherapy then they would be more suitable for carboplatin and PLDH in the platinum sensitive setting than carboplatin and paclitaxel.

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Similarly, some women have strong feelings about alopecia. Given that relapsed ovarian cancer is essentially an incurable condition, these feelings must be taken into account when helping the patient decide on a particular treatment regime.

These regimes have significant differences in terms of the various toxicities that can be expected and this to a certain extent helps the clinician tailor the treatment to the individual treatment.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

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1. Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet. 2003; **361**(9375): 2099-106.
2. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, Vasey PA, et al. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol. 2010; **28**(20): 3323-9.
3. Ledermann JA, Gabra H, Jayson GC, Spanswick VJ, Rustin GJ, Jitlal M, et al. Inhibition of carboplatin-induced DNA interstrand cross-link repair by gemcitabine in patients receiving these drugs for platinum-resistant ovarian cancer. Clin Cancer Res. 2010; **16**(19): 4899-905.
4. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. Jama. 2012; **307**(4): 382-90.
5. Kaye SB, Lubinski J, Matulonis U, Ang JE, Gourley C, Karlan BY, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal

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doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol. 2012; **30**(4): 372-9.
6. Gershenson DM, Sun CC, Bodurka D, Coleman RL, Lu KH, Sood AK, et al. Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. Gynecol Oncol. 2009; **114**(1): 48-52.