Healthcare Improvement Scotland

NICE Health Technology Appraisal On Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for recurrent ovarian cancer (inc reviews of TA91 and TA222)	
TO: NICE	**FROM: Healthcare Improvement Scotland** **18 October 2013**

Comment provided to Healthcare Improvement Scotland by:
[redacted], **Consultant Oncologist, Greater Glasgow and Clyde Health Board**

1. Do you consider that all the relevant evidence has been taken into account? ***If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?***

The data from the OCEANS study of gemcitabine, carboplatin versus gemcitabine, carboplatin and bevacizumab in platinum sensitive disease has not been considered. Bevacizumab was not considered in this assessment but the fact that gemcitabine,carboplatin and bevacizumab significantly improved PFS compared with carboplatin, gemcitabine alone which in turn increases PFS over carboplatin alone is of relevance when considering the role of carboplatin, gemcitabine and must be considered given the current conclusion that carboplatin, gemcitabine is not recommended.

There was little assessment of weekly regimens of carboplatin or cisplatin combinations or of weekly paclitaxel. There is a lack of randomised trials with these regimens but there are several trials demonstrating their efficacy and they are used regularly in clinical practice in platinum resistant disease with definite benefit. By not assessing these regimens the MTA does not reflect clinical practice

The main omission is consideration of treatment for women at second or more relapse. The evidence is limited but this makes up a major part of the clinical work load as most women will receive multiple lines of therapy and this needs to be considered in the conclusions.

2. **Do you consider that the analysis of clinical and cost effectiveness has used an appropriate comparator which reflects Scottish practice?** ***If not, please explain.***

In Scotland women with platinum sensitive relapse will receive combination platinum based therapy where their performance status allows and after discussion, they accept the increased toxicity. The choice of combination depends on prior toxicities and co-morbidities. Not all centres have access to carboplatin/PLD on their formularies, although individual requests can be made, so in these centres carboplatin/paclitaxel is standard therapy but where carboplatin/PLD is available this may be standard based on the CALYPSO trial. Women with hypersensitivity to paclitaxel or persistant neuropathy are appropriate to use single agent carboplatin as the comparator in the cost-effectiveness analysis. As a result I am not clear that it is appropriate to use single agent carboplatin as the comparator in the cost-effectiveness analysis.

In platinum resistant disease weekly paclitaxel or carboplatin and paclitaxel are often used. This was particularly the case when PLD was not available due to manufacturing problems or where it has been used in platinum sensitive disease where a weekly carboplatin/paclitaxel or weekly paclitaxel regimen may be used before topotecan (weekly) or gemcitabine. 3 weekly paclitaxel is hardly ever used in platinum resistant disease as most women have already received it in first and often in second line treatment. So I do not think this is an appropriate comparator.

3. **Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? *If not, in which areas do you consider that the summaries are not reasonable interpretations***?

The analyses are complex and sometimes difficult to follow but I do have concerns about the methodology comparing different trials that have different definitions of progression and platinum sensitivity. If progression is defined by CA125 criteria, this will result in a different population from that defined by RECIST and as a result the PFS and OS between trials may be very different. This may explain why they conclude in 4.2.14 that carboplatin/PLD is less effective and more costly than carboplatin/paclitaxel even though the CALYPSO trial, which is the only direct comparator trial, showed improved PFS with carboplatin/PLD.

Similarly the population in the carboplatin v carboplatin/gemcitabine trial was different from that of the carboplatin v carboplatin/paclitaxel in terms of the percentage that had received prior paclitaxel, which may have explained the lack of overall survival benefit in the carboplatin/gemcitabine study as this trial included more resistant tumours. It is this lack of survival benefit that seems to influence the cost-benefit analysis the most and this may not be a true reflection of the activity of the regimen.

4. The summary states that “Overall, no chemotherapy was consistently associated with either a lower risk or a higher risk of the adverse events assessed. “ Although it may be difficult to say which regimen has a higher or lower risk of adverse events, they do have very different toxicity profiles so for some women, with prior neuropathy, the risk of neuropathy may be very high and potentially devastating and similarly recurrent alopecia will be very much more difficult for some women than others. The summaries do not reflect the importance of choice for women.

5. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? *If not, why do you consider that the recommendations are not sound?*

The provisional recommendations are very limiting and do not make any reference to the treatment of women beyond their first relapse. The danger of not recommending carboplatin and gemcitabine in platinum sensitive relapse or topotecan is that it severely limits the regimens available to women for successive lines of therapy as well as limiting the choice of regimen based on toxicity. For example if a women receives carboplatin/paclitaxel first line and carboplatin/PLD for platinum sensitive recurrence what should she then receive when she develops a further recurrence, either platinum sensitive or resistant?

The recommendations are also not clear as to whether carboplatin/PLD is recommended or not in platinum sensitive relapse.

Given the improvement in efficacy with Trabectadin/PLD over PLD alone this option should be available for women with hypersensitivity to carboplatin and cisplatin.

6. **Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? *If not, how do they differ in Scotland?***

The patient pathways are applicable in Scotland. There are some differences in Scotland compared to England. Carboplatin/PLD is not routinely available in all centres for platinum sensitive treatment. Carboplatin/gemcitabine/bevacizumab is not available as it is in England via the Cancer Drug Fund.

7. **Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland?** ***If so, please describe what these changes would be.***

Yes it would significantly reduce the options for treatment available for women with recurrent ovarian cancer and potentially stop women being able to receive successive lines of therapy, the availability of which is, at least in part, responsible for the improvement in median survival seen over the last decade.

8. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? ***If yes, please explain why this is the case.***

I think the same issues are pertinent to both countries despite current differences in availability of drugs.

Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment.

I am concerned that far from progressing the care of women with recurrent ovarian cancer, this guidance is a backward step, limiting choice of therapy and the number of lines of therapy. It also comes at a time when there are a number of new agents entering the field and it would be better to wait and appraise these newer technologies rather than restricting older technologies.