Professional organisation statement template

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: R Paul Symonds. TD, MD, FRCP, FRCR
Reader in Oncology , [redacted]

[redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √ I have published more than 40 papers on the treatment of carcinoma of cervix by surgery, radiotherapy, chemoradiotherapy, chemotherapy and the epidemiology of this condition.

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √ Principal Investigator of SCOTCERV study. Principal Investigator of proposed CIRCCa study (cediranib combined with paclitaxel and carboplatin versus carboplatin and paclitaxel)

- 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.)? √ Member of NCRN Gynaecological Cancer Sub-committee. Previously Chairman of the Medical Research Council Gynaecological Cancer working party.

- other? (please specify) √ Lead Investigator, Faculty of Clinical Oncology of the Royal College of Radiologists audit of cancer of cervix treated by radiotherapy and chemoradiotherapy 2001 - 2002

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?

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?

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)?

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?

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.

Patients with recurrent carcinoma of cervix or those who present with metastatic disease (stage 4b) have a poor prognosis with a 1-year survival of between 15 and 20%. Chemotherapy is relatively ineffective in this group of patients and currently there is no current standard of care.

Scale of the problem
Both mortality and incidence of carcinoma of cervix in the United Kingdom has fallen markedly over the last 30 years. In 2005 there were 2803 new cases of cervical cancer with 949 deaths. (Cancer Research UK 2008) Approximately 1200 women a year are treated in the UK for recurrent or metastatic cervical cancer.

Cancer of cervix is more common in the Republic of Ireland and Eastern Europe. Cancer of cervix is still the most common female cancer in South Asia, South America and sub-Saharan Africa.

Practice in Britain tends to have some impact in these countries (resources permitting), especially in India.

Treatment of Primary Cancer
Between 70 and 80% of cervical cancer in England and Wales is found at stage 1 (tumour confined to cervix). Patients with micro-invasive disease may be suitable for conservative therapy although patients with cervical cancers confined to cervix up to 4cms in diameter, if fit enough, are treated by radical hysterectomy. Five-year survival for micro-invasive disease is between 97 and 100% and for those with stage 1b disease treated by radical surgery, 85%.

Locally advanced cervical tumours (stages 2a to 4a) confined to the pelvis are treated by radical radiotherapy or more recently chemoradiotherapy. The expected survival for stage 2b disease (involvement of parametrium) is 70% and for stage 3b disease (fixed to pelvic side-wall) 40 to 50%.

Since 1999 patients in the United Kingdom have been treated increasingly by chemoradiotherapy. By far the most popular regimen used is weekly cisplatin, 40mg/m^2, which is given during radiotherapy for up to 6 pulses of treatment. In a MRC meta-analysis showed a 29% reduction in the odds of death if chemoradiotherapy was given rather than radiotherapy. This would result in an absolute increase of 12% 5-year survival for a patient with stage 3b disease. [Green et al 2001]

A recent Royal College of Radiologists' audit of patients treated in 2001 and 2002 (1200 patients) has shown an improvement in 5-year survival, particularly for stages 2 and 3, compared to patients treated in 1993.

It should be noted most patients now receive cisplatin, the most effective chemotherapeutic agent against cervical cancer, as part of their primary treatment.

Current Practice
Until 2005 the most common regimen used to treat recurrent or advanced cervix cancer was cisplatin. A dose of 50mg/m^2 given 3 weekly was thought to be a good compromise balancing efficacy against side-effects. Until 2005 no combination was shown to be superior to weekly cisplatin.

Gynaecology Oncology Group (GOG) Trials 169/179
The GOG trial 179 was instrumental in topotecan being licenced for use in cervical cancer [Long et al 2005]. 146 patients were randomised to receive cisplatin and 147 cisplatin and topotecan. There was a statistically significant improvement in objective response rate with the combination arm. 27% of the combination arm patients had an objective response compared to 13% of patients receiving cisplatin alone (p = 004). The median overall survival was improved in the combination group which was 9.4 months versus 6.5 months for those receiving only cisplatin (p = 0.017). The benefit from the combination of cisplatin and topotecan was most apparent in patients who had a long disease-free interval from primary therapy and those who had not received prior cisplatin. 57% of patients in GOG179 had previously been treated with cisplatin-based chemoradiation. The median survival for those that received no prior cisplatin was 15.4 months with the combination of topotecan plus cisplatin versus 7.9 months for those who received prior cisplatin-based chemoradiotherapy. The probability of survival increased incrementally for both treatment groups the longer the patient was from prior cisplatin therapy. There was little benefit seen for patients who relapsed within 6 months of prior therapy and the greatest benefit was for those who had relapsed more than 2 years from prior cisplatin.

In Long's paper the authors arbitrarily divide the patients into those who relapsed before 16 months from primary treatment and those after and there is a statistically significant difference in survival favouring the group of patients who relapsed more than 16 months after treatment.

The trial has been widely heralded as the first trial that showed the advantage for a combination compared to single agent cisplatin. The median difference in progression-free survival being 4.6 months and for survival 2.9 months respectively.

However, it is worth comparing the survival of patients in the combination arm and those with cisplatin with an earlier GOG trial (GOG169) which was a comparison of paclitaxel plus cisplatin to cisplatin alone. [Moore et al 2004] Survival curves for those patients receiving the combination of cisplatin and paclitaxel and cisplatin and topotecan are superimposable. Unlike GOG179 there was no statistically significant difference in overall survival for the combination compared to single agent cisplatin in GOG169. The reason for the difference in survival for patients receiving cisplatin in GOG169 compared to 179 may reflect the difference in the number of patients who received prior cisplatin, usually in combination with radiation, and may reflect a higher percentage of cisplatin resistant patients in GOG179 compared to GOG169.

Toxicity for the combination of topotecan plus cisplatin was significant with 70% experiencing grade 3 or 4 neutropenia and 18% febrile neutropenia. None of these toxicities resulted in treatment related death and a parallel quality of life study revealed no adverse effects of the increased toxicity on patients' quality of life.

GOG Study 204

This study has not been published in full but was presented at ASCO in 2008 [Monk et al]. This is a randomised phase III trial of four cisplatin-containing doublet combinations in patients with stage 4b recurrent or persisting cervical cancer. A total of 513 patients were randomised to combinations of cisplatin and paclitaxel, cisplatin and vinorelbine, cisplatin and gemcitabine and cisplatin and topotecan. The four arms of the study were fairly well randomised to factors such as median age, time to recurrence, performance status and previous chemoradiotherapy that might have altered outcome. The response rates for cisplatin and paclitaxel was 21.9%, cisplatin and vinorelbine 25.9%, cisplatin and gemcitabine 22.3% and cisplatin and topotecan 23.4%. There was a modest progression-free survival advantage in the order of 6 weeks between the best performing arm of the study (cisplatin and paclitaxel) and the worst (cisplatin and gemcitabine). The difference in median overall survival was of the same order of magnitude between the best and worst arms of the study. Partially because of the relative lack of toxicity and partially because of the slightly better response rate and survival, cisplatin and paclitaxel has been chosen as the control arm for the next GOG study.

SCOTCERV

SCOTCERV is the only current British phase II trial of chemotherapy in cervical cancer. Two groups were treated, 1 were patients with extra-pelvic disease as it was expected that response rates would be higher in this group of patients (29 patients). The other group (21 patients) had recurrence within the irradiated pelvis only. The combination of docetaxel and gemcitabine was chosen as this would avoid the possibility of cisplatin resistance following previous cisplatin-based chemoradiotherapy. Many patients who have a relapsed carcinoma of cervix have impaired renal function owing to tumour pressing on the ureters. Both docetaxel and gemcitabine have predominantly non-renal routes of excretion therefore impaired renal function would not be a contra-indication for treatment in this group of patients. At the time of writing the trial is closed and the results are being analysed at the Cancer Research UK Clinical Trials Office in Glasgow. A preliminary analysis has shown a response rate of 30% with a median survival of 9 months. Further information may be available by the May 21st meeting of NICE.

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?

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.

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?

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?

Advantages
Topotecan has been licenced in the treatment of carcinoma of cervix and has been marketed on a basis that a combination of cisplatin and topotecan is the only combination of therapy that has been shown to extend life (albeit modestly) in recurrent carcinoma of cervix. This has been clearly shown in GOG179.

Disadvantages
If one compares progression-free and overall survival in the older GOG169 trial, for patients receiving cisplatin and paclitaxel, survival is virtually identical to those in the combination arm of GOG179. The major difference between the trials is the survival of patients in the control arm (cisplatin). This probably reflects the different levels of cisplatin resistance within the 2 groups of control patients.

It is an undeniable fact the majority of patients now who proceed to chemotherapy for persisting or recurrent cervix cancer have already received cisplatin as part of a chemoradiotherapeutic regimen. GOG179 undoubtedly shows that patients pretreated with cisplatin have a worse overall outcome than those who are chemotherapy naïve. A combination of cisplatin and topotecan gives more haematological toxicity than cisplatin alone. The combination induced substantial neutropenia in 70% of patients compared to only 1.4% of patients receiving cisplatin. 18% of patients in the combination arm had febrile neutropenia. However, as the authors of GOG179 point out these complications were manageable with antibiotics, protocol specific dose modifications and the addition filgrastim on subsequent treatment cycles.

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)?

There is no standard chemotherapy for patients with relapsed carcinoma of cervix. Virtually no regimen gives a response rate >30%. The median survival in studies is in the order of 9 months. A variety of regimens are in use within the UK. These include cisplatin, cisplatin and topotecan and carboplatin and paclitaxel.

The regimen of paclitaxel and carboplatin is widely used in the treatment of ovarian cancer and increasingly to treat recurrent endometrial cancer. There are no randomised studies to justify its use in carcinoma of cervix but there are a number of small phase II studies that report response rates of up to 50% with this combination.

A combination of topotecan and cisplatin is undoubtedly effective in some patients with metastatic or recurrent cervical cancer although GOG204 has shown that it is not superior and may be inferior to other cisplatin-based combinations of two drugs. This combination is most likely to work in patients who present with stage 4 disease and have not received previous chemoradiotherapy or those who relapse more than 16 months after chemoradiotherapy. Undoubtedly there is a high demand for treatment for patients with recurrent or persisting carcinoma of cervix and unfortunately there is no obviously best combination of chemotherapy available for such unfortunate patients. Topotecan and cisplatin is a possible treatment for these individuals. The CIRCCa trial of the anti-VEGF inhibitor cediranib in combination with

paclitaxel and carboplatin or paclitaxel and carboplatin alone has been approved by CTAAC and funding has been secured. The ideal situation would be that patients with recurrent or metastatic disease should go into this study although an alternative regimen needs to be available for patients who decline to enter a clinical trial.

References

Green JA, Kirwan JJ, Tierney JF et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: A systematic review and meta-analysis. Lancet 2001; 358: 781-6

Long HJ, Bundy BN, Grendys EC et al. Randomised Phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A Gynecologic Oncology Group study J Clin Oncol 2005; 23: 4626-4633

Moore DH, Blessing JA, McQuellon RP et al. Phase III study of cisplatin with or without paclitaxel in Stage IVb recurrent or persistent squamous carcinoma of the cervix: A Gynecologic Oncology Group study J Clin Oncol 2004; 22: 3113-3119

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