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: [redacted] **submitting on behalf of:**

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

Comments coordinated by [redacted]

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.)? X
- other? (please specify)

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?

Transitional Cell Carcinoma (TCC) of the urothelium is the 4th most common cancer in men and the 12th most common cancer in women. It is the 6th most common cause of cancer mortality in men and the 11th in women. Approximately 9000 patients are diagnosed with urothelial TCC and approximately 5000 patients die each year from it in the UK.

Patients with (Stage T2-4,N0-1,M0) may be treated with potentially curative intent by radical surgery (nephrectomy/nephroureterectomy or cystectomy +/- urethrectomy) or with radical radiotherapy (for muscle-invasive TCC of bladder). Chemotherapy may be given before (neoadjuvant) or after (adjuvant) surgery/radiotherapy in an attempt to improve cure rates in this setting.

However, many patients present with disease too advanced to be treated with curative intent, or are medically unfit for radical treatment. Furthermore, of those patients treated with curative intent, approximately 50% of patients with T2 disease, 75% of patients with T3 disease and most patients with T4 or N1 disease will subsequently recur with metastatic disease in distant lymph nodes, viscera (liver/lung notably) or bone. Chemotherapy can be given in this setting to improve quality of life and survival. The most frequently used first line chemotherapies in this setting are cisplatin/gemcitabine and carboplatin/gemcitabine. Combinations of methotrexate, vinblastine, doxorubicin and cisplatin [MVAC]; or, less commonly, gemcitabine and paclitaxel may also be used. Tumour responses are seen in approximately 50% of patients and whilst there are a small number of long term survivors following this first-line palliative chemotherapy (5-10%, mainly those with good initial performance status and without visceral metastases), the majority of patients relapse within 3 years and the median survival of these patients is 12-18 months. Estimated 25 patients/million population/year treated with 1st line platinum-based chemotherapy in UK.

When urothelial TCC progresses after 1st line platinum-based chemotherapy there is currently no single treatment that would be considered a standard second line therapy for these patients and there is variation across UK practice. Many patients have poor performance status and standard of care for them is Best Supportive Care with symptom control +/- palliative radiotherapy. For patients who are fit for 2nd line chemotherapy, a number of options exist: Although some patients are treated with Best Supportive Care alone, the majority of patients fit for further chemotherapy would be offered a second line chemotherapy regimen. For patients who had a good response to first line platinum-based chemotherapy and a long disease-free interval (>6-12 months), some oncologists would repeat the initial chemotherapy regimen. Another option is to use an alternative platinum-based regimen (e.g. MVAC if cisplatin/gemcitabine was the first-line regimen, or vice-versa). Frequently the 2nd line platinum-containing agent is carboplatin rather than cisplatin since renal function has often deteriorated at this stage and carboplatin is less nephrotoxic. Other frequently

used options in the UK include platinum/taxane combinations, single agent gemcitabine, single agent taxanes. Ifosfamide, topotecan, oxaliplatin, pemetrexed and others have also been trialled in phase 2 studies though are rarely used in the UK.

These are all alternatives to Vinflunine for second line treatment of urothelial TCC progressing after platinum-based chemotherapy. Although Vinflunine is the only agent, to date, to have shown a possible survival advantage in a phase 3 setting it was compared against Best Supportive Care. Phase 3 trials have not yet been completed in the other agents it is possible that some of them are more efficacious or less toxic than Vinflunine. Vinflunine's single agent response rate in the phase 2 setting (17%) was not markedly better than many of the other agents listed above (e.g. gemcitabine 13%, pemetrexed 8-29%, ifosfamide 20%, docetaxel 13%[Cancer 2008;113:1284–93]).

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?
Patients with poorer performance status and visceral metastases (cw node-only metastases) have a worse prognosis. There are early suggestions that some cancers with altered protein/growth factor expression may influence cancer growth rates and potentially survival outcomes but this remains investigational. The Vinflunine phase 3 trial was limited to patients with ECOG PS0 -1 and creatinine clearance ≥40mls/min; 90% of urothelial TCC deaths occur in patients >65 years and many older patients have comorbidities precluding first or 2nd line chemotherapy (cardiorespiratory or poor renal function). Smoking-related comorbidities are more frequent in patients with urothelial TCC since it is a risk factor for the development of these cancers. The incidence of bladder cancer in poorer socioeconomic groups is increased as result of smoking and industrial exposure to carcinogens. Prior pelvic irradiation resulted in increased haematological toxicity from Vinflunine and requires dose reduction.

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)?
Vinflunine is delivered intravenously over a twenty minute infusion. It is a vesicant drug with potential to cause severe soft tissue damage at the injection site if drug escapes outside the vein. For this reason it is likely to be delivered only in specialist oncology chemotherapy clinics. The staff and expertise would be routinely available in this setting and no additional input would be required.

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?
Not applicable

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.
No guidelines in existence.

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?

There is clearly an unmet need for second line treatments for patients with urothelial TCC progressing after platinum-based chemotherapy. Any positive phase 3 study in this domain is welcomed.

Easier/More difficult: There has been limited experience in the use of Vinflunine in patients with urothelial TCC in the UK. The anecdotal experience of the urological oncology community in the UK and Europe is that this is not one of the easier drugs to deliver to patients as a result of its toxicity profile. In the phase 3 trial constipation, (47.6%), stomatitis (28.6%) and myalgia (16.1%) were the main excess adverse events attributed to Vinflunine. The main excess grade 3 or 4 adverse events were constipation (16.1%), anaemia (19.8% vs 8.1%) and neutropenic sepsis (6%).

A number of the other agents presently used in the second-line setting are reasonably well tolerated and, in phase 2 studies, appear to have similar response rates. For this reason, even if available, should the issues relating to toxicity be borne out, alternative second line treatments may be preferred.

Practical implications:

The vesicant nature of Vinflunine means that there are likely to be a very small number of patients suffering soft tissue damage at the infusion site, occasionally requiring surgical intervention. In the phase 3 study, Vinflunine was associated with a 6% neutropenic sepsis rate, 19% grade 3/4 anaemia, 16% grade 3/4 constipation rate. Additional clinical events and costs would be associated with these events. Whilst there may be similar rates of these events associated with the other currently used second line chemotherapies, the phase 3 trial compared Vinflunine against Best supportive Care (and since both arms of the trial went on to have similar rates of other chemotherapies (~30% in both arms) these would be additional costs rather than comparative to another chemotherapy.

If comparing to Best Supportive Care, treatment with Vinflunine will require all of the usual facilities required for the delivery of an outpatient chemotherapy regimen.

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.

As with other chemotherapies, would anticipate regular cross sectional imaging (usually CT) to assess response prior to initiation and approximately every 2-3 cycles thereafter. May require formal renal function assessment before initiation (e.g. EDTA creatinine clearance).

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?

There is a single randomised phase 3 study for this technology. This has been discussed at a NCRI bladder cancer chemotherapy subgroup meeting (Chairman; Dr John Chester). There are some question marks surrounding the design (lack of placebo control, unrepresentative performance status restrictions), analysis (per protocol rather than intention to treat), side effect profile, low response rates and clinical vs statistical significance of any benefits:

Patients included may not be representative of the majority of patients progressing after first line therapy; they were required to have ECOG PS0-1 with creatinine clearance ≥40mls/min and the phase 3 study also appears to have excluded patients who had received prior neoadjuvant or adjuvant platinum-based chemotherapy (~50% of patients treated with radical surgery or radiotherapy will receive this).

Thus, many patients progressing after platinum-based chemotherapy would not fit into these categories. For those that do fulfil these criteria, there is variation in national practice but Best Supportive Care is not necessarily appropriate for all patients in this category - many patients in the UK would be offered 2nd line chemotherapy as above. Thus the control arm in this phase 3 trial (Best Supportive Care) may not be representative for all patients in this category.

Although there is not phase 3 data to show that any of these other agents/regimens produce a survival benefit in the second-line setting, the phase 2 data of many of them is comparable to or better than Vinflunine. Thus it cannot be ruled out that one or more of these other regimens are more efficacious or less toxic than Vinflunine.

A number of statistical analyses of the Vinflunine phase 3 trial were performed. For the intention to treat (ITT) population, the control group median survival was 4.6 months and the Vinflunine arm was 6.9 months but this was not statistically significant (p=0.287). A multivariate analysis on the ITT population correcting for prognostic factors was statistically significant (p=0.036). A number of patients in both arms were incorrectly entered into the trial (mainly patients who had previously received neoadjuvant or adjuvant chemotherapy – not allowed in the study) and when these patients were excluded from the analysis the median survivals of 6.9 months (Vinflunine) and 4.3 months (Best Supportive Care) were statistically significant (p=0.04).

The consensus of the NCRI group was that this available data does not definitively show Vinflunine to be superior to other currently available approaches and is not sufficient to justify the routine use of Vinflunine outside of a clinical trial. Most UK urological non-surgical oncologists would not currently regard Vinflunine as the standard second-line agent of choice in progressive urological TCC.

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 the phase 3 trial constipation (47.6%), stomatitis (28.6%) and myalgia (16.1%) were the main excess adverse events (of any grade) attributed to Vinflunine. The main excess grade 3 or 4 adverse events were constipation (16.1%), anaemia (19.8% vs 8.1%) and neutropenic sepsis (6%). Only 58% of patients received >90% of the planned Vinflunine dose. Very little quality of life data is available from the phase 3 trial. It is stated that Vinflunine did not induce a decrease in health-related quality of life when compared with BSC alone using a composite end point based on

PS, weight, pain index, EORTC QLQ C30, analgesic consumption and use of palliative radiotherapy. The relative weighting of each of these factors is not detailed. 23% of patients in the Best Supportive Care arm received radiotherapy compared to 4% in the Vinflunine arm; however, the study was not placebo-controlled and the treating clinician may have been more inclined to offer earlier palliative radiotherapy to those in the control arm for whom no other active treatment (chemotherapy) was being given. This may reflect clinician behaviour rather than patients' quality of life and it would be interesting to compare the QoL data elements separately.

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.

None

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)?

Vinflunine should be able to be delivered within the existing NHS facilities/resources. It would require no new infrastructure/equipment and would contribute proportionally to staff and facilities running costs.