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]

Name of your organisation: Royal College of Pathologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- 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)

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.

The management of MDS is generally unsatisfactory, and there is currently no licensed or 'gold standard' treatment for any type of MDS. The literature abounds with small uncontrolled studies, usually detailing the short term response to a wide variety of agents. There is also a dearth of randomised trials such that the relative merit of various forms of treatment remains unclear. This lack of good trial data in a relatively common disorder with a short median survival reflects both the difficulty of trial design and the disappointing preliminary results obtained with most currently available treatments but is largely due to the advanced age of most of the patients, whose general health, social situation and own wishes and expectations are major factors in determining appropriate treatment. Management options range from observation only, supportive care, 'active treatment' (low dose chemotherapy, intensive chemotherapy, stem cell transplantation), to symptom relief only for patients whose general health is so poor that an improvement in their haematological status would confer no corresponding improvement in quality of life. Identification of risk factors for disease progression and use of the IPSS score to predict outcome may help guide the clinician in deciding patient management. The British Committee for Standards in Haematology have published guidelines for the treatment of MDS, but these are now out of date and precede the use of Azacitidine.

Supportive Care:

Because the majority of MDS patients are old and often have additional medical problems, the current standard of care for 'older' patients has generally been accepted as supportive care, which includes blood product transfusions for symptomatic anaemia or thrombocytopenic bleeding.

Low-Intensity Therapy:

Low-intensity therapy includes the use of low dose chemotherapy or biologic response modifiers. The UK national AML 14 trial showed that in elderly AML patients, low dose Cytarabine had superior overall survival rates than oral chemotherapy (hydroxycarbamide). Although this type of treatment is mainly provided in the outpatient setting, supportive care or hospitalisation (for example, treatment of infections) may often be needed, as cytopenias can still be profound. These agents are often administered in the context of clinical trials because for most drugs, little is known about the efficacy, optimal doses, toxicity, or the appropriate selection of patients. The National Acute Myeloid Leukaemia trial (AML 16), is looking further into treatment options for older patients with high risk MDS or AML.

High-Intensity Therapy

High-intensity therapy includes intensive induction chemotherapy and haematopoietic stem cell transplantation. Although these approaches have a greater chance of changing the natural history of the disease and potential cure, they also have an attendant greater risk of regimen-related morbidity and mortality. Patients with MDS treated with intensive chemotherapy have lower complete remission rates, higher relapse rates, shorter periods of remission and a greatly increased risk of aplastic death than similar patients with de novo AML.

Transplantation

Stem Cell transplantation (SCT), the only known curative modality in MDS, is an option for few patients (probably around 10%) because of older age, co-morbidities, or lack of a donor. Currently, about one-third of MDS patients who undergo bone marrow transplants may be cured, but around 25-35% die from complications. Work is ongoing to investigate the use of reduced intensity allografts (so called ‘mini’ transplants) as opposed to standard conditioning transplants. This approach will reduce transplant related mortality but at the expense of higher relapse rates.

Conclusion

Given the limitations of existing therapies, MDS remains a condition where a significant number of patients can only expect to receive supportive care. This gives a prognosis to high risk patients of only 4 months. There is a clear need for an effective therapeutic option for patients with MDS, which can be well tolerated in an outpatient setting with an emphasis on quality of life.

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?

From personal experience, the drug is very easy to give and well tolerated. It requires similar concomitant medications as low dose chemotherapy with no additional clinical requirements.

In our hands, the disease response is assessed after 4 cycles. If the disease has progressed and the patient is no longer benefiting from the treatment, it is discontinued.

Myelodysplasia is incurable, except in patients successfully treated with a stem cell transplant. The most important outcome measure is overall survival and quality of life. The recently published trial: Efficacy of Azacitidine compared to conventional care regimens in the treatment of higher-risk myelodysplastic syndromes – a randomised, open label, phase III study (Fenaux P et al, Lancet Feb 2009), shows a survival benefit.

QOL has been investigated by Kornblith AB *et al*; Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. J Clin Oncol. 2002;20:2441-52. The results of this study showed that patients on the azacitidine arm experienced significantly greater improvement in fatigue (EORTC, *P* 0.001), dyspnea (EORTC, *P* 0.0014), physical functioning (EORTC, *P* 0.0002), positive affect (MHI, *P* 0.0077), and psychological distress (MHI, *P* 0.015) over the course of the study period than those in the supportive care arm.

The drug seems very well tolerated. If the injection site reaction becomes a significant problem, the drug can be delivered intravenously. Nausea and bowel irregularities are easily managed/prevented. Grade 3-4 cytopenias are seen with its use but similarly they are seen with intensive and low dose chemotherapy.

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.

No

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)?

No extra training would be required. If the treatment protocol of 75mg/m^2 days 1-7 is followed, aseptic pharmacy would need to reconstitute the drug at weekends as it has a very short expiry time once made up. This facility is not available at many UK hospitals at present.