

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.

<p>About you</p> <p>Your name:</p> <p>Comments submitted by [REDACTED], [REDACTED] on behalf of:</p> <p>Name of your organisation Royal College of Physicians / National Cancer Research Institute/Royal College of Radiologists/Joint Collegiate Council for Oncology/Association of Cancer Physicians</p> <p>Submission coordinated by: [REDACTED]</p> <p>Are you (tick all that apply):</p> <ul style="list-style-type: none">- a specialist in the treatment of people with the condition for which NICE is considering this technology? <input checked="" type="checkbox"/>- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? <input checked="" type="checkbox"/>- 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.)? <input checked="" type="checkbox"/> [REDACTED] and [REDACTED]- other? (please specify)
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What is the expected place of the technology in current practice?

The poor prognosis of this group of patients, coupled with the relatively older age at presentation (70-75 years) has created a therapeutic nihilism in the UK for the management of high-risk MDS. The advent of a new agent that is well tolerated and highly efficacious is most welcome and is already creating a huge upsurge in interest for the management and research of this rare but difficult disease. The current management strategies available in the NHS reflect the “conventional care regimens” (CCR) within the AZA 001 study which confirms the efficacy of azacitidine in these patients (Fenaux et al, Lancet Oncology 2009 epub Feb 18th). The proportion of patients treated with each of the three conventional care regimens in the 001 study approximately reflects everyday practice with the majority of patients treated with best supportive care, fewer with low dose chemotherapy such as low dose cytarabine and fewer still with intensive chemotherapy. Those suitable for intensive chemotherapy will be relatively younger and fitter, and will include some with an option for further attempted curative treatment in the form of allogeneic stem cell transplantation. This approach culminating in allogeneic stem cell transplantation is the only curative option for such patients and will continue to be, as these patients are appropriately excluded from the licensed indication for azacitidine. Despite these interventions the overall survival of the CCR group in the 001 study was only 15 months.

There is considerable variation in prognosis within the subgroups of patients for whom azacitidine is licensed in Europe, ranging from <6 months untreated for IPSS High MDS to approximately 12-18 months for IPSS INT-2 and CMML-2. Nevertheless, analysis of the benefit for azacitidine across all of these subgroups in the 001 study has demonstrated a survival advantage for all subgroups when treated with azacitidine (Fig 4, Fenaux et al, Lancet Oncology 2009 epub Feb 18th). There is no evidence that toxicity varies between these subgroups.

Azacitidine is currently administered within the secondary care sector but there are already pilot projects exploring use in the homecare setting in the UK. Administration in France is almost exclusively in the homecare setting. Monitoring will continue to be from the secondary sector for the management of the mild myelosuppression. Other non-haematological toxicities are mild and easily managed.

Most UK haematology centres are already familiar with using azacitidine. Specialist centres for MDS such as ours have been treating patients within the licensed indication subgroups for 1-2 years, and a large number of UK centres have been administering azacitidine within the AML16 NCRI clinical trial.

The European LeukemiaNet guidelines for the diagnosis and management of myelodysplastic syndrome are in their final draft stage and will be finalised by the guidelines group at the international MDS scientific meeting in Patras, Greece in May 2009. This group has used the rigorous guideline methodology for the Italian Society of Haematology comprising comprehensive literature review, scenario setting and analysis and three consensus conferences to produce the final draft. Please see below for the draft recommendations pertaining to azacitidine. The British Society for Standards in Haematology guidelines for the diagnosis and management of MDS will be updated to reflect these European guidelines later in the summer. This group is chaired by Dr David Bowen (our nominated clinical expert for this technology)

The advantages and disadvantages of the technology

The high proportion of patients currently treated with best supportive care reflects the lack of an available, tolerable and efficacious therapeutic option for the majority of patients for whom intensive chemotherapy is inappropriate and low dose chemotherapy of only limited efficacy. Azacitidine will dramatically change this, with its good safety profile and considerable efficacy. All but the most elderly / infirm patients will potentially be eligible for active treatment with azacitidine. The survival advantage for azacitidine is very considerable for a condition with such a poor prognosis. Survival with azacitidine is doubled at 2 years compared with the CCR alternatives. In addition, clinically very relevant advantages for azacitidine are the considerable prolongation in the time to transformation to acute myeloid leukaemia and more importantly still, the high frequency of patients becoming free from blood transfusions (45%). Quality of life has previously been demonstrated to be significantly improved by azacitidine in a phase 3 US study.

Azacitidine clearly has different practical challenges from the CCR regimens. Patients will have one or two subcutaneous injections daily for 7 days repeated every 4-6 weeks and will require blood count monitoring between courses, at least during the first few cycles. The incidence of side effects is low, with the highest frequency being subcutaneous erythematous reactions. We have not found this to be problematic provided patients receive reassurance and provided patient and staff education is good. Once familiar with the drug, these reactions become routine. Gastrointestinal toxicity is almost always mild and easily managed. Quality of life on azacitidine is improved compared with best supportive care in clinical trials. The main practical difficulty is administration at weekends and centres will require aseptic pharmacy and nursing support at weekends to manage this. The major challenge in the homecare setting will be administration over the weekend but pilot projects of mobile aseptic units are set to overcome this. Alternative schedules appear equally efficacious but these are currently outside the licensed scheduling (Lyons et al, Journal of Clinical Oncology 2009 epub Mar 2).

There are no extra blood or bone marrow tests required prior to treatment over and above standard care. The duration of therapy has some important implications. Firstly the pharmacodynamics of activity of azacitidine is unlike other drugs used to treat the myeloid malignancies. Patients may only start to respond after up to 6 courses of therapy and indeed in the large US trials, 10% responders did so after course 6. Thus it is imperative that patients are treated with a full 6 courses of azacitidine before response can be meaningfully assessed. Responding patients must continue treatment until loss of response, progression or death. The median number of cycles administered in the 001 study was 9. There are no data to indicate that it is safe or sensible to stop therapy in responding patients.

Finally, the 001 trial was carefully designed to reflect real clinical practice, hence the choice of CCR as the comparator after much debate. The proportion of patients treated with the different CCR regimens broadly reflects UK practice. The trial clearly analysed the most important outcomes and the primary endpoint of overall survival advantage was comfortably achieved. The relevant secondary endpoints of time to AML transformation and red cell transfusion dependence were assessed. Although patient reported outcomes were unfortunately not assessed, these data are fortunately available from the large US phase 3 study (Kornblith et al, Journal of Clinical Oncology 2002, 20, 2441)

Any additional sources of evidence

The final draft European LeukemiaNet guideline has the following **draft** guidance for the use of hypomethylating agents including azacitidine:

The Expert Panel agreed on the following recommendations:

- *Patients with intermediate-2 or high IPSS risk disease who are not eligible for AML-like chemotherapy should be treated with azacitidine (Recommendation level B);*
- *Fit patients with intermediate-2 or high IPSS risk and poor risk cytogenetics who lack a stem cell donor should receive treatment with azacitidine (Recommendation level B)*

Implementation issues

There would be no significant requirement for additional training as most haematology units will already have experience with azacitidine as indicated above. No new equipment is required.