Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Lenalidomide for the treatment of myelodysplastic syndromes associated with a deletion 5q cytogenic abnormality in people with red blood cell transfusion dependence

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: Comments submitted by [redacted], [redacted] on behalf of:

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

Comments coordinated by Professor David Bowen

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)?
- other? (please specify)

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What is the expected place of the technology in current practice?

The indication for lenalidomide therapy will be red cell transfusion dependent patients with low risk or Intermediate-1 (INT-1) risk Myelodysplastic Syndrome (MDS) defined by the International Prognostic Scoring System (IPSS) associated with a deletion (del) 5q31 cytogenetic abnormality.(1) This latter component may be defined as patients with an isolated del(5q31) abnormality or with one additional cytogenetic abnormality. **Demographics:** Low risk and INT-1 MDS with del(5q) is a small subgroup of MDS patients representing around 4% all newly diagnosed MDS patients (6% low-risk and INT-1 patients) with an incidence of 0.15 per 100,000. Median age at diagnosis is 74yrs. Approximately 75-100 new patients will be diagnosed in the UK per annum. Only half of newly diagnosed patients will be dependent upon red blood cell transfusions at diagnosis but the majority of patients will develop transfusion-dependency during the course of their disease.(2)
Prognosis: The median survival of this subgroup of patients is circa 6 years. Patients dependent upon red cell transfusion (the target population for lenalidomide treatment) have a poorer prognosis than those not requiring transfusion (44mo vs 97mo). 18% all patients will develop acute myeloid leukaemia (AML) by 5 years. Patients with increased bone marrow blasts (5-10%) have a shorter survival than those with <5% blasts.(2)
Current treatment: Red cell transfusion is the mainstay for those patients with symptomatic anaemia. Many guidelines also recommend iron chelation therapy although the evidence base for this intervention is lacking. No high quality studies of the efficacy and safety of chronic red cell transfusion have been conducted and as such there is no evidence base for quality of life and clinical efficacy of this intervention. Personal observation would indicate that red cell transfusion produces periods of better QoL but a cyclic lifestyle based around the peaks and troughs of the transfusion cycle. Iron chelation therapy will usually have a negative impact on short-term QoL but is putatively investing in a reduction of longer-term complications. A small proportion of patients (with serum erythropoietin concentration < 500 IU/l) will be eligible for a trial of Erythropoietic Stimulating Agent (ESA) and 46% such patients will respond with an improvement in haemoglobin concentration for a median duration of 13 months.(3) ESA is administered by weekly or 2-3 weekly subcutaneous injection with a good side effect profile. Thalidomide may be useful with a 35% response rate for duration of 9 months but this is rarely used in UK practice.(3) Thalidomide has a poor side effect profile. Younger patients (generally <60y) with heavy red cell transfusion dependence are candidates for allogeneic stem cell transplantation although numerically these are very few; the mortality from this procedure is up to 25% but those that survive are mainly cured of their MDS, as relapse rates are low.
There should be no significant geographical variation or indeed divergences of opinion between clinicians given the paucity of current therapeutic options available. The only geographical variation is that some regions will have lenalidomide on the list of approved agents for the Cancer Drugs Fund and others will not.

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Lenalidomide should only be used in the secondary care setting in centres familiar with myelosuppressive chemotherapy. In contrast to its use in myeloma, lenalidomide is often profoundly myelosuppressive when used to treat MDS with del(5q31). Weekly blood counts must be performed for at least the first three cycles of therapy, by the end of which most responders will have achieved a response. There is no role for shared care with the community services.

The technology is available via the CDF in some regions of England and via Individual Funding Requests to NHS funding organisations (PCTs in England). There is wide geographical variation in current access. There should be little use of lenalidomide outside its licensed indication. There are data to support clinical activity for single agent lenalidomide in high-risk MDS and AML with del(5q31) but no randomised controlled trials have been performed to date.

Clinical Guidelines: Lenalidomide is licensed in the US for the indication currently under consideration by NICE. The US MDS guidelines (NCCN) recommend use of lenalidomide within its US licenced indication. The European LeukemiaNet European MDS guidelines are at the final draft stage, as are the revised British Committee for Standards in Haematology (BCSH) MDS guidelines.

The advantages and disadvantages of the technology

Clinical trial data: All studies of lenalidomide in the treatment of MDS with del(5q31) have reported efficacy (transfusion independence). There are no meaningful data for QoL or for survival. It is unclear if the achievement of transfusion independence is a surrogate for improved survival in low-risk MDS. The patient populations in all clinical trials of lenalidomide for low-risk MDS with del(5q31) have been reasonably representative, with a lower median age than the unselected datasets as is always the case. The only large multicentre trial (Celgene 004) was an RCT of placebo versus lenalidomide at two different doses.(1) Non-responders crossed over at 16 weeks. 56% patients in the 'higher' dose lenalidomide arm became red blood cell transfusion independent (TI) and the median duration of transfusion independence was not reached. A previous study (Celgene 003) indicates median transfusion independence duration of just over 2 years.(4) As such, for responders this is a potentially meaningful treatment, at least for the duration of TI. The recommended starting dose is now 10 mg daily. Given that 95% responders have responded after 3 cycles of therapy, this could reasonably be the recommended duration of therapeutic trial.(1)
Predictive factors for response: There is only one consistent clinical parameter that predicts for response to lenalidomide, namely platelet count >150 x 10^9/l. Patients with over-expression of P53 and/or mutation/deletion of the *TP53* gene have a higher rate of transformation to AML and a poorer survival. Patients with mutation / deletion of *TP53* have a poor response to lenalidomide therapy.(5) However the assay systems for detection of such abnormalities of *TP53* are very difficult to standardise both for sensitivity and specificity in routine clinical practice

Safety: The principal reason why lenalidomide was not licensed in Europe whilst receiving an MA in the US was concern regarding safety. It had appeared that the rate of transformation to AML in patients treated in the phase 2 studies with lenalidomide was higher than expected. In addition, data for an increased risk of second primary malignancy (SPM) with lenalidomide exposure were emerging in myeloma. Finally in myeloma, lenalidomide (plus dexamethasone) was associated with an increased rate of venous thromboembolism. Thus far, there is no evidence for an increase in SPM in MDS patients treated with lenalidomide, and although there may be a slightly increased risk of venous thrombosis this is not really clinically important given the magnitude of benefit.(1)
Retrospective studies have recently been published that are somewhat reassuring regarding the risk of AML transformation with lenalidomide therapy, within the usual limitations of retrospective comparisons.(6, 7) However the rate of AML transformation in the RCT Celgene 004 study at 22-30% at 5 years is of concern given that data from the pre-lenalidomide era would indicate an AML transformation rate of 17% at that time point. There are many caveats to this latter comparison, principally that patients entered into the Celgene 004 study were not newly diagnosed, although the pre-lenalidomide data indicate that most AML transformations occur relatively early (before 3 years) in red cell transfusion dependent patients.(2) Non-responders to lenalidomide have a higher AML transformation rate but this may reflect disease biology.(8) On balance the data are more reassuring that lenalidomide does not increase the transformation rate to AML and the EMA will only licence this drug if they are also reassured about this important issue.

In summary, lenalidomide is an efficacious therapy for achieving TI in transfusion dependent low-risk MDS patients with del(5q31) either as an isolated abnormality or with a single additional cytogenetic abnormality. Patients with platelet count >150 x 109/l respond more frequently and patients with abnormalities of P53 respond poorly. Standardisation of techniques to assay P53 dysfunction will be challenging. No data are available to confirm benefit for QoL or for overall survival.

Any additional sources of evidence

There are two databases that could potentially provide information about the management and outcome of such patients namely:
1. Haematological Malignancies Research Network (HMRN) based at University of York. The manufacturers will probably try to access these data
2. The European LeukemiaNet (ELN) low-risk MDS Registry coordinated by University of Nijmegen, The Netherlands. Prof Bowen is the Co-Chair of the Steering Committee for this programme.

Both datasets are reasonably high quality and record routine management of unselected patients from the relevant participant sites. HMRN registers all haematological malignancies from a population of 3.5 million since 2004. ELN

registers all patients with low-risk MDS from >100 sites across 11 European countries since 2008 (n=1300 currently).

Implementation issues

The patient population eligible for this technology is small. There is no additional resource required in units providing this treatment but they must be familiar with the use of myelosuppressive therapy and able to support patients with significant cytopenias.

Equality

The patient population for this technology is a) older and b) has a female preponderance.
The decision to offer patients this technology would have to involve a judgement as to whether achieving transfusion independence would improve that individual's QoL. Unfortunately there are no objective, validated tools available to aid in that judgement which inevitably will be subjective and dependent upon the experience of the prescribing physician.

References

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