NICE National Institute for Health and Care Excellence

NICE guidance

Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant

Technology appraisal guidance
Published: 5 August 2020

www.nice.org.uk/guidance/ta640

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Treosulfan with fludarabine is recommended as an option for conditioning treatment before allogeneic haematopoietic stem cell transplant (allo-HSCT) for people with malignant diseases for whom a reduced intensity regimen, such as low-dose busulfan with fludarabine, would be suitable.

Why the committee made these recommendations

People with malignant diseases having an allo-HSCT need to have conditioning treatment first to prepare their bone marrow. If they cannot tolerate high-intensity myeloablative conditioning, they can have reduced-intensity conditioning such as low-dose busulfan with fludarabine.

The clinical evidence compares treosulfan and fludarabine with low-dose busulfan and fludarabine. Not enough evidence was presented for children or for people who could tolerate a high-intensity myeloablative regimen, so it is not possible to make recommendations for these groups.

The evidence in people for whom reduced-intensity is the most appropriate conditioning regimen shows that people are less likely to die from the transplant or associated complications if they have treosulfan and fludarabine instead of busulfan and fludarabine. The risk of disease recurrence was similar after either treatment.

Treosulfan with fludarabine is more effective and costs less than low-dose busulfan with fludarabine in most analyses. Therefore, treosulfan with fludarabine is recommended as an option in the NHS for conditioning treatment for people who would normally have a reduced intensity regimen.

2 Information about treosulfan

Marketing authorisation indication

2.1 Treosulfan (Trecondi, Medac) in combination with fludarabine (generic) is indicated 'as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than 1 month with malignant diseases'.

2.2 This appraisal focuses on malignant diseases only.

Dosage in the marketing authorisation

2.3 The dosage schedule for treosulfan is available in the summary of product characteristics.

Price

2.4 Treosulfan:

- £494.40 per 5-vial pack of 1 g powder for solution for injection (BNF online accessed December 2019)
- £2,434.25 per 5-vial pack of 5 g powder for solution for injection (BNF online accessed December 2019).

2.5 Fludarabine:

- £155.00 per vial of 50 mg powder for solution for injection (BNF online accessed November 2019).

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Medac, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that 1 issue was resolved during the technical engagement stage and agreed that it is reasonable to assume that allogeneic haematopoietic stem cell transplantation (allo-HSCT) practice is similar in England and Wales to other European countries.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 36), and took these into account in its decision making. It discussed the following issues (issues 1, 2, 3, 5 and 6), which were outstanding after the technical engagement stage.

Treatment pathway and clinical need

Conditioning treatment is an essential but traumatic step before allo-HSCT

3.1 Allo-HSCT is a potentially curative therapy for more than 70 malignant diseases, such as acute myeloid leukaemia. Before having the transplant, people have conditioning treatment to prepare their bone marrow. Conditioning treatments are usually chemotherapy alone or chemotherapy with radiotherapy. High-intensity myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) are 2 types of regimens. The clinical expert explained that the RIC regimens are usually interchangeable, and the commonest regimens are busulfan with fludarabine and melphalan with fludarabine. MAC regimens differ more and are associated with a higher toxicity. Therefore, MAC regimens would only be offered to people who are fit and healthy enough to tolerate them. The patient experts explained that the allo-HSCT process is long and involves an extended stay in hospital. They explained that

conditioning treatment is a traumatic experience and can have a substantial psychological impact. Conditioning drugs given before a transplant remove the recipient's haematopoietic cells from the bone marrow. This can have powerful effects on the body. For many patients, the conditioning treatment is more challenging than the chemotherapy they have previously had. Transplant-related complications include increased mortality, graft-versus-host disease (with symptoms such as mouth blisters or skin rashes) and infections such as shingles or pneumonia. The clinical expert explained that it typically takes 12 to 24 months to recover from a transplant and for the immune system to recover. The committee concluded that conditioning treatment for allo-HSCT is an important part of the procedure that can be difficult to tolerate, but it is necessary to remove any remaining disease and prepare the bone marrow to receive and accept the transplant.

There is a clinical need for effective conditioning treatments with reduced transplant-related toxicity

3.2 The clinical expert's written submission explained that conditioning treatments have a major impact on the success of the transplant. They are designed to reduce the risk of disease recurrence or rejection of the graft by the body. The transplant itself carries short- and longer-term risks in terms of mortality and morbidity. The aim is to minimise these, while not compromising the success of the transplant. Conditioning treatments therefore have an impact on the patient's survival, quality of life and wellbeing. Both the physical and major psychological effects of a transplant were particularly highlighted by the patient experts. The clinical expert explained that all conditioning treatments have immediate major side effects, but that they are essential for a successful transplant. The treatment must ablate the marrow enough to remove remaining disease and allow the transplant to be accepted. But it must also not be so toxic that the patient dies of transplant-related causes such as infection. The committee concluded that patients and healthcare professionals would welcome conditioning regimens that allow a successful transplant with reduced risks.

Clinical evidence from MC-FludT-14-L trial 2

MC-FludT-14-L trial 2 reflects UK allo-HSCT clinical practice

3.3 MC-FludT-14-L trial 2 is a double-blind randomised clinical trial of treosulfan and fludarabine compared with low-dose busulfan and fludarabine in adults with acute myeloid leukaemia or myelodysplastic syndromes who were not eligible for high-intensity MAC regimens. No UK patients were included in the trial, and most patients were from Germany. The company explained that clinical practice in the UK is similar to that in other European countries included in the trial. In addition, 50 UK transplant centres are members of the European Society for Blood and Marrow Transplantation (EBMT) and work according to the EBMT guidelines. The clinical expert explained that the target population for treosulfan in the UK would be similar to the population in the trial; that is, people who would not be eligible for high-intensity MAC regimens. The committee concluded that allo-HSCT practice in MC-FludT-14-L trial 2 is comparable to clinical practice in the UK for that group of people.

Treosulfan with fludarabine reduces mortality relative to low-dose busulfan with fludarabine

3.4 Treosulfan is an alkylating agent. The company proposes it as a reduced-toxicity MAC, with lower toxicity than usual MAC regimens. The primary endpoint of MC-FludT-14-L trial 2 was event-free survival. This composite endpoint defined an event as disease relapse, graft failure or death, whichever occurred first. Event-free survival at 24 months was 65.7% in the treosulfan arm and 51.2% in the busulfan arm (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.49 to 0.84). The disaggregated event-free survival results showed that the main benefit of treosulfan was on mortality, especially non-relapse mortality. It had limited effect on disease relapse rates. Relapse rates were 22.8% in the treosulfan arm and 25.4% in the busulfan arm (HR 0.82, 95% CI 0.59 to 1.16), death rates were 13.1% in the treosulfan arm and 19.8% in the busulfan arm (HR 0.63, 95% CI 0.41 to 0.97). The company explained that this is because of lower non-relapse mortality rates with treosulfan: patients are less likely to die from the transplant, associated infections or graft-versus-host

disease. In the trial, the main causes of non-relapse deaths were infections and graft-versus-host disease (both causes combined: 13.9% for treosulfan compared with 21.5% for busulfan). The committee concluded that people eligible for low-dose busulfan with fludarabine have a lower mortality with treosulfan and fludarabine than with low-dose busulfan and fludarabine.

Benefit and risk of increased toxicity have to be balanced in conditioning regimens

3.5 The committee heard that treosulfan is considered a reduced-intensity conditioning (RIC) regimen according to the European public assessment report, although the company stated that treosulfan is a reduced-toxicity MAC regimen. In MC-FludT-14-L trial 2 the treosulfan dose was reduced from 14 mg per m^2 to 10 mg per m^2 because of increased infections after treosulfan treatment. The clinical expert believed that the 10 mg per m^2 dose of treosulfan used in the trial was myeloablative although there is no clear-cut threshold for when a regimen becomes myeloablative. The main clinical consideration is toxicity. The benefit of reduced relapse needs to be balanced with the increased risk of death from toxicity. The committee concluded that the balance between benefit and risk is an important consideration for conditioning regimens.

Cost effectiveness

The company's economic model is suitable for decision making

3.6 The company submitted a partitioned survival model to estimate the cost effectiveness of treosulfan and fludarabine compared with low-dose busulfan and fludarabine. The committee considered that the model is suitable for decision making.

Assuming a 5-year cure point to model mortality is plausible

3.7 The company used a cure point to model mortality, based on the rationale that allo-HSCT is potentially curative. In the company's base case, a fixed cure point of 5 years was assumed for people who had not

relapsed 5 years after transplantation. The company explained that patients who survive allo-HSCT for at least 5 years are considered cured in clinical practice. The ERG tested the impact of changing the cure point. Results were similar to the base-case analysis except when the cure point was assumed to be 1 year, when treosulfan with fludarabine was dominated by busulfan with fludarabine (that is, it was less effective and cost more). The clinical expert explained that relapse is likely to occur in the first and second year after allo-HSCT, and that a cure point of 5 years was a robust assumption. The committee concluded that it was reasonable to assume that people who have not relapsed within 5 years of the transplant can be considered cured.

Treosulfan with fludarabine is cost effective compared with low-dose busulfan with fludarabine, in patients otherwise eligible for low-dose busulfan with fludarabine

3.8 Treosulfan with fludarabine dominates busulfan with fludarabine; that is, it generates more quality-adjusted life years (QALYs) at a lower cost than busulfan in both the company's base case and ERG's preferred assumptions analyses. The committee concluded that treosulfan with fludarabine is cost effective compared with low-dose busulfan with fludarabine, in people who would otherwise be eligible for low-dose busulfan with fludarabine.

Evidence in other patient populations

3.9 The committee considered the evidence for:

- people who could tolerate high-intensity MAC regimens
- children.

The committee could not make a positive or negative recommendation for these groups, which were not included in MC-FludT-14-L trial 2, because it needed more comparative evidence. The committee invites the company to provide more evidence.

The evidence is only in people ineligible for high-intensity MAC

3.10 The company submitted evidence based on MC-FludT-14-L trial 2, in which the patient population was not eligible for a high-intensity MAC regimen. The trial used 1 comparator, the reduced-intensity regimen of low-dose busulfan and fludarabine. Therefore, the company's submission only partially addressed the NICE scope, which included high-intensity regimens such as cyclophosphamide and irradiation, cyclophosphamide and busulfan. No evidence was submitted on treosulfan and fludarabine compared with other conditioning regimens (particularly high-intensity MAC regimens) and in patients who can tolerate high-intensity MAC regimens. The company explored 2 approaches to generate comparative evidence with other regimens, using registry analyses and indirect treatment comparison. The committee understood that randomised controlled trials were available, and some indirect treatment comparisons were feasible. However, the company did not include any indirect comparisons in the submission because it considered that they were unlikely to be reliable. The committee concluded that it could not make a positive or negative recommendation for people who could have a high-intensity MAC regimen because no comparative evidence was supplied.

The only evidence in children is from a single-arm trial

3.11 The clinical evidence for treosulfan in children was from the single-arm MC-FludT-17-M trial, which showed low mortality rates at 100 days and high overall survival and event-free survival at 12 months. No evidence of the efficacy of treosulfan in children compared with other regimens was submitted. The committee considered the evidence presented, and the apparent favourable outcomes in the single-arm trial. But the company did not attempt to compare the outcomes from the treosulfan-based regimen against those that might be expected with existing treatments. There was also no evidence presented on the relative costs of the alternatives. In the absence of any evidence on the relative clinical and cost effectiveness of a treosulfan-based regimen compared with other regimens, the committee could not make a recommendation, either positive or negative, about the use of treosulfan in conditioning regimens for children.

Conclusion

Treosulfan with fludarabine is clinically and cost effective as conditioning treatment before allo-HSCT for people with malignant diseases in whom a reduced-intensity regimen would be appropriate

3.12 Treosulfan with fludarabine is associated with reduced toxicity and mortality compared with a reduced-intensity regimen comprising low-dose busulfan with fludarabine. Treosulfan with fludarabine has been shown to be more effective and cost less than low-dose busulfan with fludarabine in people with malignant disease who would otherwise have a reduced-intensity conditioning regimen. Therefore, treosulfan with fludarabine is recommended as an option for conditioning treatment before an allo-HSCT for people with malignant diseases who would otherwise be eligible for low-dose busulfan with fludarabine.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient is going to have an allo-HSCT and the doctor responsible for their care thinks that treosulfan with fludarabine is the right conditioning treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Caroline Bregman
Technical lead

Rufaro Kausi
Technical adviser

Thomas Feist
Project manager

ISBN: 978-1-4731-3824-7

Accreditation