NICE National Institute for Health and Care Excellence

NICE guidance

Gemtuzumab ozogamicin for untreated acute myeloid leukaemia

Technology appraisal guidance
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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 Gemtuzumab ozogamicin, with daunorubicin and cytarabine, is recommended as an option for untreated de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, in people 15 years and over, only if:

- they start induction therapy when either the cytogenetic test confirms that the disease has favourable, intermediate or unknown cytogenetics (that is, because the test was unsuccessful) or when their cytogenetic test results are not yet available and
- they start consolidation therapy when their cytogenetic test confirms that the disease has favourable, intermediate or unknown cytogenetics (because the test was unsuccessful) and
- the company provides gemtuzumab ozogamicin according to the commercial arrangement.

1.2 These recommendations are not intended to affect treatment with gemtuzumab ozogamicin that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For young people aged 15 to 17, this decision should be made jointly by the young person and their parents or carers and the clinician.

Why the committee made these recommendations

AML is currently treated with daunorubicin plus cytarabine. Cytogenetic testing is used to look for specific gene mutations in certain types of leukaemia, which might predict how a person's disease responds to treatment and affect treatment options. People whose disease has favourable or intermediate cytogenetics have a better prognosis than those whose disease has unfavourable cytogenetics in terms of treatment response, risk of relapse and survival. However, for some patients the cytogenetic test results are not available at the start of induction treatment.

Evidence from a randomised clinical trial shows that, for people whose disease has favourable or intermediate cytogenetics, gemtuzumab ozogamicin with daunorubicin and

cytarabine is more clinically effective than daunorubicin and cytarabine. People are more likely to live longer without the disease relapsing or symptoms returning.

Because no clinical- or cost-effectiveness analysis is presented for people whose disease has unfavourable cytogenetics, gemtuzumab ozogamicin cannot be recommended for this group.

The most plausible cost-effectiveness estimates (including the stopping rule for consolidation therapy in people who have unfavourable cytogenetics) for gemtuzumab ozogamicin compared with daunorubicin and cytarabine in people whose disease has favourable, intermediate or unknown cytogenetics (because the cytogenetic test is unsuccessful) are within the range that NICE normally considers an acceptable use of NHS resources. Therefore gemtuzumab ozogamicin can be recommended for these groups of people.

2 Information about gemtuzumab ozogamicin

Marketing authorisation indication

2.1 Gemtuzumab ozogamicin (Mylotarg, Pfizer) is indicated 'for the treatment of previously untreated, de novo CD33-positive acute myeloid leukaemia, except acute promyelocytic leukaemia for patients age 15 years and above, in combination with daunorubicin and cytarabine.'

Dosage in the marketing authorisation

2.2 The gemtuzumab ozogamicin dose is 3 mg/m^2/dose (up to a maximum of 1×5-mg vial) infused over a 2-hour period. Induction: gemtuzumab ozogamicin 3 mg/m^2/dose (up to a maximum of 5 mg/dose) given on days 1, 4 and 7. Consolidation courses 1 and 2: gemtuzumab ozogamicin 3 mg/m^2/dose (up to a maximum of 5 mg/dose) given on day 1 of each course.

Price

2.3 The list price for gemtuzumab ozogamicin is £6,300 per 5-mg vial (excluding VAT; BNF online [accessed August 2018]). The company has a commercial arrangement. This makes gemtuzumab ozogamicin available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Pfizer and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

New treatment option

People with acute myeloid leukaemia would welcome a new treatment option

3.1 Acute myeloid leukaemia (AML) is a rapidly progressing form of leukaemia. People with the disease have fatigue, weakness or breathlessness, memory loss, bruising, bleeding and frequent infections. There is a poor prognosis for patients whose disease does not respond to treatment, or whose disease responds then relapses. The committee agreed that new treatments, which could improve the chance of successfully inducing first remission would be welcomed.

Clinical management

Current treatment for AML is daunorubicin plus cytarabine and this is the appropriate comparator

3.2 The aim of intensive chemotherapy is to induce complete remission. After this people would have either consolidation chemotherapy or a stem cell transplant. Most patients with AML in the UK are entered into the National Cancer Research Institute AML trials; AML 19 for younger patients and AML 18 for patients over 60 years. Both trials currently include gemtuzumab ozogamicin as an induction therapy for patients without a known adverse karyotype at diagnosis. Outside of clinical trials, most patients for whom intensive chemotherapy is considered suitable currently have standard combination chemotherapy (daunorubicin plus cytarabine) without the addition of gemtuzumab ozogamicin. Intensive treatment

for AML is essentially unchanged in 40 years. Although survival has gradually improved this has been largely a result of improvements in supportive care and decision-making about when to have allogeneic stem cell transplant. The committee concluded that established clinical management is daunorubicin plus cytarabine and this is the relevant comparator for this appraisal.

Cytogenetic testing is standard clinical practice in England

3.3 Everyone with newly diagnosed AML has cytogenetic testing because this provides important information about prognosis and how the disease might respond to different treatments. People who have AML with favourable or intermediate cytogenetics have a better prognosis than those whose disease has unfavourable cytogenetics. The committee understood that larger centres have placed great emphasis on obtaining the cytogenetic results as quickly as possible, usually within days. However in smaller centres, it may take between 1 and 3 weeks to obtain the results. The clinical experts confirmed that cytogenetic testing takes between 7 to 10 days and it would be challenging to reduce this to less than 7 days. The committee acknowledged that cytogenetic testing is standard clinical practice and confirmed its importance in the clinical management of untreated AML.

Cytogenetic test results are not always available at the start of the induction treatment

3.4 Some patients need to start treatment urgently before cytogenetic results have been received. The clinical experts at the first committee meeting explained that around 15% to 20% of patients have a very high or rapidly increasing white blood cell count, evidence of tumour lysis or disseminated intravascular coagulation, or life-threatening bleeding or infection when they are diagnosed. They also explained that for this group of patients there is no evidence to suggest that starting treatment before cytogenetic results are available is harmful. Treatment would be stopped if the tests revealed that the patient had AML with unfavourable cytogenetics. In response to consultation, consultees emphasised the importance of patients with AML having treatment within a week of their diagnosis. One of the consultees highlighted that 32% of patients with AML start

treatment on the day of diagnosis and a further 47% start treatment within a week of their diagnosis. The committee accepted that the proportion of patients who have to start treatment urgently before cytogenetic results have been received (approximately 80%) was much higher than the 15% to 20% initially considered at the first committee meeting. The committee acknowledged the importance of being able to start treatment for these people before cytogenetic test results are available. It agreed to explore the effect of including the costs that would be incurred in patients who need urgent treatment while waiting for cytogenetic results and who were later found to have unfavourable cytogenetics (see section 3.5) and to take this into account in its decision-making (see section 3.16).

Population

The population specified in the company's decision problem is appropriate

3.5 The committee considered the population relevant to this appraisal and noted that the marketing authorisation does not define the population by cytogenetic status. But the company's base case focused on patients whose disease was not known to have unfavourable cytogenetics. This included people whose disease had favourable, intermediate or unknown cytogenetics. The committee was aware from responses to consultation that approximately 20% of patients have favourable cytogenetics, 60% have intermediate cytogenetics and 20% have unfavourable cytogenetics. The clinical experts supported the company's rationale for excluding patients whose disease had unfavourable cytogenetics because these patients have a worse prognosis (see section 3.3). The committee recalled that patients who have AML with favourable or intermediate cytogenetics have a better prognosis than those whose disease has unfavourable cytogenetics (see section 3.3). It was also aware that there was a subgroup of patients with unknown cytogenetics in the company's base case. This subgroup could include those for whom treatment was started before the test results had become available (see section 3.4) and those for whom the testing was unsuccessful in determining cytogenetic status. The clinical experts explained that if the testing was unsuccessful, it was not routine clinical practice to re-test.

The committee understood that an element of clinical judgement was needed when offering treatment to these patients but they would generally have the same treatment as those with favourable or intermediate cytogenetics. The committee concluded that the population specified in the company's decision problem was appropriate.

Clinical evidence

The results from ALFA-0701 are generalisable to clinical practice in England

3.6 ALFA-0701 (n=271) was an open-label, phase 3, randomised controlled trial, done across 26 haematology centres in France. It included patients aged 50 to 70 years with previously untreated de novo (that is, it excluded secondary leukaemia) AML. The trial compared gemtuzumab ozogamicin plus daunorubicin and cytarabine with daunorubicin and cytarabine alone. The data presented were from the 30 April 2013 data cut and the committee stated that a more recent data cut from ALFA-0701 trial would be informative. The population covered by the marketing authorisation was extended to include people aged 15 to 17 years and restricted to de novo CD33-positive AML. Most patients diagnosed with AML are over 50 years. Therefore, the population included in the trial is likely to reflect most patients for whom gemtuzumab ozogamicin would be suitable in clinical practice. The trial did include a small number of patients whose disease was not CD33-positive, who would not have gemtuzumab ozogamicin according to the marketing authorisation. The committee agreed that it can only appraise gemtuzumab ozogamicin within its marketing authorisation. It concluded that ALFA-0701 trial is generalisable to the population who would have gemtuzumab ozogamicin plus daunorubicin and cytarabine in clinical practice in England.

The dosing schedule in ALFA-0701 differs from the dose in ongoing trials in the UK

3.7 The dosage for gemtuzumab ozogamicin in ALFA-0701 is in line with the marketing authorisation. However, the 2 ongoing UK trials (AML 18 and AML 19)

use a different dosage. Therefore, the granting of the marketing authorisation may have implications for practice, because UK clinicians are currently using the dosage used in AML 18 and AML 19, rather than the licensed dosage. The committee agreed that it could only recommend gemtuzumab ozogamicin in line with the dosage specified in the marketing authorisation.

The individual patient data meta-analysis may not be generalisable to clinical practice in England

3.8 The main clinical evidence was supported by an individual patient data meta-analysis. However, the meta-analysis included patients aged 15 years or over with newly diagnosed de novo or secondary AML or high-risk myelodysplastic syndrome. This is a broader population than the marketing authorisation. The committee concluded that the results may not be generalisable to people who would have gemtuzumab ozogamicin in clinical practice in England.

Clinical-effectiveness results

Gemtuzumab ozogamicin increases event-free survival and relapse-free survival compared with chemotherapy

3.9 The company reported outcomes assessed by investigator and by independent review committee. The analysis by independent review committee was considered to be academic-in-confidence by the company and cannot be reported here. Because the analyses by investigator assessment are reported in the summary of product characteristics, those results are reported here. The primary outcome measure in ALFA-0701 was event-free survival. An event was defined as induction failure, relapse or death. Treatment with gemtuzumab ozogamicin plus daunorubicin and cytarabine increased median event-free survival compared with daunorubicin and cytarabine alone. The analysis by investigator assessment shows increased median event-free survival from 9.5 months to 17.3 months (hazard ratio [HR] 0.56; 95% confidence intervals [CI] 0.42 to 0.76, p=0.0002). Relapse-free survival and overall survival were secondary end points. Median relapse-free survival increased from 11.4 months

to 28 months (HR 0.53; 95% CI 0.36 to 0.76, p=0.0006) in patients who had gemtuzumab ozogamicin plus daunorubicin and cytarabine. Median overall survival increased from 21.8 months to 27.5 months (HR 0.81; 95% CI 0.60 to 1.09, p=0.165). However, the difference between treatment groups did not reach statistical significance. The committee concluded that gemtuzumab ozogamicin plus daunorubicin and cytarabine was clinically effective compared with chemotherapy.

Gemtuzumab ozogamicin increases event-free survival and relapse-free survival in the combined favourable and intermediate cytogenetic group but not in the unfavourable group compared with chemotherapy

3.10 The company reported outcomes assessed by investigators and by independent review committee, categorised by cytogenetic profile. The analysis by independent review committee was considered to be academic-in-confidence by the company and cannot be reported here. Because analyses by investigator assessment are reported in the summary of product characteristics, those results are reported here. Gemtuzumab ozogamicin plus daunorubicin and cytarabine increased median event-free survival from 12.2 months to 22.5 months (HR 0.49; 95% CI 0.33 to 0.72, p=0.0003) in those whose disease had favourable or intermediate cytogenetics. There was no statistically significant difference in median event-free survival in patients whose disease had unfavourable cytogenetics (from 2.8 months to 4.5 months [HR 1.111; 95% CI 0.63 to 1.95, p=0.72]). For patients whose disease had favourable or intermediate cytogenetics, overall survival increased from 26.0 months to 38.6 months (HR 0.747; 95% CI 0.511 to 1.091, p=0.1288). For patients whose disease had unfavourable cytogenetics, overall survival decreased from 13.5 months to 12.0 months (HR 1.553; CI 0.878 to 2.748, p=0.1267). The committee concluded that gemtuzumab ozogamicin plus daunorubicin and cytarabine compared with chemotherapy was clinically effective for patients whose disease had favourable and intermediate cytogenetics. Also, results from those subgroups were better than for the overall population, but only when results from patients with unfavourable cytogenetics were excluded.

There is heterogeneity in the clinical outcomes in the intermediate cytogenetic subgroup

3.11 The company provided additional analyses for the intermediate cytogenetic group by cytogenetic and molecular risk profile (that is, for intermediate-1 and intermediate-2 subgroups). The company reported outcomes by independent review committee only. The analysis was considered to be academic-in-confidence by the company and cannot be reported here. The ERG highlighted the differences in the clinical benefit seen in patients whose disease had an intermediate-1 or intermediate-2 cytogenetic and molecular risk profile. The committee acknowledged that results for the intermediate-2 group were based on small numbers of patients. The committee concluded that the results highlighted heterogeneity in the clinical outcomes in the intermediate group. Therefore it agreed to account for this in its decision-making (see section 3.24).

The intermediate-1 and -2 cytogenetic subgroup classification system is outdated

3.12 The clinical experts explained that the classification of intermediate-1 and intermediate-2 by cytogenetics only is outdated, and a new classification is being used in clinical practice. This updated classification takes account of more genetic abnormalities such as abnormalities in FLT3, NPM1, CEBPA and other genes. In response to consultation, the company highlighted that although clinicians may consider the intermediate-1 and -2 classification outdated, the intermediate-1 subgroup accounts for two-thirds of the total patients expected to have treatment in clinical practice. The committee concluded that, although the clinical results are different between intermediate-1 and -2, it would prefer not to split the intermediate group using an outdated classification system.

Gemtuzumab ozogamicin is generally well tolerated

3.13 There was an increase in veno-occlusive disease in patients taking gemtuzumab ozogamicin plus daunorubicin and cytarabine compared with those taking daunorubicin and cytarabine alone. However, the numbers of patients who had other adverse effects were similar between the 2 groups. The committee

concluded that gemtuzumab ozogamicin was generally well tolerated.

The risk of developing veno-occlusive disease is low

3.14 The patient organisation stated that the risk of veno-occlusive disease appeared to be relatively low when gemtuzumab ozogamicin doses of 3 mg/m^2 or less are used with standard therapy as part of initial therapy for AML. This is in line with the dosage in the marketing authorisation and in ALFA-0701. The clinical experts confirmed that it was a rare side effect but clinicians are experienced in managing it. The committee concluded that the risk of developing veno-occlusive disease because of gemtuzumab ozogamicin was low.

Company's economic model

The model is complex and appropriate for decision-making

3.15 In its original submission, the company presented a semi-Markov cohort state-transition model with 12 health states. The main effectiveness data came from ALFA-0701. It was used to estimate overall survival and relapse-free survival, using mixture cure models fit to Kaplan–Meier data. The committee was aware that there was no explicit structural link between a number of key model parameters, including between relapse and haematopoietic stem cell transplant; the model structure was complex and challenging to critique. However, the committee concluded that model was appropriate for decision-making.

The company updated its model and cost-effectiveness analyses after the second appraisal committee meeting

3.16

Survival modelling

People who have not relapsed after 5 years are considered to be cured

3.17 In its original submission, the company assumed that patients who were alive after 5 years from the start of the gemtuzumab ozogamicin treatment were considered to be functionally cured. The clinical experts confirmed that if patients have not had a haematopoietic stem cell transplant and have not relapsed within 5 years, they would be considered cured. The clinical experts also estimated that relapses between 3 and 5 years are rare; they happen in less than 5% of AML patients. The committee concluded that using 5 years as a cure point was appropriate.

Survival curves for people considered to be cured are appropriately modelled

3.18 In its original submission, the company explored various alternative approaches for extrapolating survival data. It explored a range of mixture cure model survival functions and concluded that the log-normal and Weibull models showed the best statistical and visual fit. The difference in the cure fraction between treatment groups was broadly similar for both the mixture cure model log-normal and Weibull functions for both event-free survival and overall survival. The ERG noted that this was important because the difference between the groups is the main driver of differences in the quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) estimates. The committee concluded that the company's approach to curve fitting and the rationale for selecting the log-normal function in its base case was appropriately justified.

A mortality risk higher than that for the general population is appropriate for patients who are considered to be cured

3.19 In its original submission, the company calculated an increased mortality risk for functionally cured patients compared with the general population. The company

considered the increased mortality risk to be academic-in-confidence and therefore it cannot be reported here. The ERG noted that in some years the probability of death was still higher for the general population than for the functionally cured patients. The ERG adjusted the mortality calculations so that the mortality risk for functionally cured patients was always higher than for the general population. This increased the hazard ratio. The committee agreed that the ERG's hazard ratio was more plausible. In response to consultation and in the analyses provided after the second appraisal committee meeting (see section 3.16), the company re-estimated its base-case mixture cure curves with background mortality based on the lifetables (Office of National Statistics, 2017). The committee considered this amendment to be reasonable and noted that it had little effect on the ICER.

Utility values in the model

Patients considered to be cured would have a lower quality of life than that of the general population

3.20 The company used utility values from literature sources, because information on health-related quality of life was not collected as part of ALFA-0701. In the economic model, the company assumed that functionally cured patients have the same health-related quality of life as the general population. The ERG used lower utility values for functionally cured patients. The committee considered the ERG's approach to be reasonable and that this was consistent with the assumption that functionally cured patients have a higher mortality risk than the general population (see section 3.19). The committee concluded that the ERG's alternative utility values were the most plausible. After the second appraisal committee meeting, the company presented a scenario analysis with an alternative utility value of 0.77 (from NICE's technology appraisal guidance on azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts) compared with that used by the ERG (0.74) and 0.74 for the complete remission health state. The committee considered that the company's alternative utility value was reasonable and noted that it had little effect on the ICER.

A stopping rule for people who have treatment before cytogenetic test results are available

A stopping rule is appropriate for people who need gemtuzumab ozogamicin induction therapy before their cytogenetic test results are available

3.21 The committee recalled that some patients might need urgent treatment, which would involve starting gemtuzumab ozogamicin without their cytogenetic test results being available (see section 3.4). It also recalled that urgent therapy was needed if the patient had a very high white blood cell count, a rapidly increasing white blood cell count, evidence of tumour lysis with or without disseminated intravascular coagulation or had life-threatening bleeding or infection (see section 3.4). The committee was aware that the treatment costs for patients who need urgent treatment while waiting for their cytogenetic test results and who were later found to have unfavourable cytogenetics were not included in the company's original economic model. Including them may result in an increase in the ICER. The committee agreed that in clinical practice, patients would have gemtuzumab ozogamicin with the first course of chemotherapy while waiting for their cytogenetic results. Treatment with gemtuzumab ozogamicin should only be continued after induction therapy (that is consolidation therapy) for patients whose disease did not have unfavourable cytogenetics. The committee concluded that it was appropriate to include a stopping rule in the cost-effectiveness analyses for people who need urgent treatment with gemtuzumab ozogamicin before cytogenetic test results are available.

The company's approach to modelling the stopping rule is appropriate for decision-making

3.22 To address the committee's concerns about the potential effect of including the costs that would be incurred in patients who need urgent treatment while waiting for cytogenetic test results and who were later found to have disease with unfavourable cytogenetics, the company did a revised analysis after the second appraisal committee meeting (see section 3.16). In this analysis, 100% of patients

were assumed to have disease of unknown cytogenetic status and were given 1 cycle of induction therapy with gemtuzumab ozogamicin. The analysis further assumed that, at the time a decision is made to proceed (or not) with consolidation therapy, cytogenetic status would be known and only patients with disease of favourable and intermediate cytogenetics would continue gemtuzumab ozogamicin consolidation therapy. To support the above assumption, the company noted that the time lag between induction and consolidation therapies is approximately 3 months. In the revised analysis, it was assumed that 21% of patients would have disease with unfavourable cytogenetics, based on the distribution observed in ALFA-0701. The cost of providing gemtuzumab ozogamicin consolidation therapy was adjusted accordingly by excluding the costs of consolidation therapy for this proportion of patients. The clinical-effectiveness data for gemtuzumab ozogamicin for this analysis was based on the 'all patient' survival analysis. It was assumed that gemtuzumab ozogamicin would not provide any clinical benefit for patients whose disease had unfavourable cytogenetics. Therefore removing the consolidation courses would not be expected to change incremental QALYs. The committee noted the ERG's critique of the company's implementation of the stopping rule. It was aware of the ERG's concerns about the company's comment that only patients who had disease with known favourable and intermediate cytogenetics would continue with gemtuzumab ozogamicin consolidation therapy, and that this appeared to exclude consolidation treatment for patients with disease with unknown cytogenetics because the cytogenetic test was unsuccessful (see section 3.5). The committee also noted the ERG's comment that the company's revised analysis actually assumed that patients would continue with consolidation therapy only if they were known not to have unfavourable cytogenetics (that is, including people who had disease with favourable, intermediate or unknown cytogenetics because the cytogenetic test was unsuccessful). The committee agreed that the company's interpretation was consistent with the committee's preferred stopping rule and that the company's approach to modelling the stopping rule was appropriate for its decision-making.

Cost-effectiveness results

The most plausible ICER for the company's base-case population (including the stopping rule) is below £20,000 per QALY gained

3.23

The ICER for people whose disease has intermediate cytogenetics is below £30,000 per QALY gained

3.24 The committee was aware of the ERG's concerns about heterogeneity in the clinical outcomes in the subgroup whose disease had intermediate cytogenetics (see section 3.11). This subgroup was included in the company's original base-case analysis. At the first appraisal committee meeting the committee considered the ERG's original exploratory analyses, which explored the effect of the heterogeneity on the ICERs. The committee noted that the deterministic ICER for the subgroup of patients whose disease had intermediate cytogenetics only was £31,709 per QALY gained, but that it was lower for the subgroup of patients whose disease had intermediate-1 molecular status (£16,343 per QALY gained). It agreed that it was reasonable to assume that the heterogeneity in the clinical outcomes was leading to the higher ICER for the intermediate cytogenetic group. The committee recalled that the clinical experts explained that such classification of the intermediate group was not being used in clinical practice and that it had concluded not to split the intermediate cytogenetic group using an outdated classification system (see section 3.12). The committee therefore agreed that the most relevant ICER for its decision-making was the ICER for the intermediate group, which was £31,709 per QALY gained. The committee considered the company's additional cost-effectiveness analysis for the intermediate cytogenetic group provided after the second appraisal committee meeting (see section 3.16). The committee noted that the probabilistic list price ICERs were £33,683 per QALY gained or £32,991 per QALY gained, depending on whether they were based on the ERG's original proposed parameter inputs only or with the company's 2 additional amendments (see section 3.16). The committee was aware that the company had provided probabilistic ICERs for these analyses incorporating a simple discount patient access scheme (the ICERs incorporating the patient access scheme are confidential and cannot be reported here). The

committee noted the ICERs decreased when the gemtuzumab ozogamicin patient access scheme was taken into account. It concluded that the most plausible ICER for the intermediate group was below £30,000 per QALY gained.

It is not appropriate to consider the subgroup of patients with unfavourable cytogenetic status

3.25 The committee was aware that neither the company nor the ERG had presented clinical- or cost-effectiveness evidence for the subgroup of patients whose disease had unfavourable cytogenetic status. The committee recalled that the clinical experts' comments and the consultation comments supported the company's rationale for excluding patients whose disease had unfavourable cytogenetics (see sections 3.3 and 3.5). In the response to consultation, a consultee highlighted that a meta-analysis by Hills et al., which was based on ALFA 0701, AML 15 and 16, showed that gemtuzumab ozogamicin should not be given to patients whose disease is known to have unfavourable cytogenetics. The committee agreed that it was not appropriate to consider the subgroup of patients whose disease had unfavourable cytogenetics in its recommendations.

Innovation

There are no additional benefits that are not captured in the QALY calculations

3.26 The company considered gemtuzumab ozogamicin to be an innovative treatment because when used with daunorubicin and cytarabine it extends the duration of remission. It works in a novel way to directly target CD33-positive AML blasts and induce leukaemia cell death. The committee concluded that gemtuzumab ozogamicin would be beneficial for patients, but it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

End of life

Gemtuzumab ozogamicin does not meet the criteria to be considered a life-extending treatment at the end of life

3.27 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. This states that a treatment can be considered as a 'life-extending treatment at the end of life' if it is indicated for patients with a short life expectancy, normally less than 24 months, and it offers an extension to life, normally of a mean value of at least an additional 3 months compared with current NHS treatment. The committee noted that the results of ALFA-0701 showed that gemtuzumab ozogamicin could increase life expectancy compared with standard care by more than 3 months. However, the short life expectancy criterion was not met (company model: standard care life years gained was 6.02).

Conclusion

Gemtuzumab ozogamicin is recommended for routine use for disease with cytogenetics that are favourable, intermediate or unknown (because the test was unsuccessful)

3.28 The committee concluded that gemtuzumab ozogamicin, plus daunorubicin and cytarabine, was clinically effective compared with chemotherapy (see sections 3.10 and 3.11). The committee was aware that some patients need gemtuzumab ozogamicin before cytogenetic test results are available (see section 3.21). The committee concluded that patients should have gemtuzumab ozogamicin induction therapy while waiting for their cytogenetic results. Gemtuzumab ozogamicin should only be continued after induction therapy (that is consolidation therapy) for patients whose disease has favourable or intermediate cytogenetics, confirmed by cytogenetic testing, or unknown cytogenetics (because the cytogenetic test was unsuccessful; see section 3.21). The most plausible cost-effectiveness estimates for gemtuzumab ozogamicin for people whose disease has favourable, intermediate or unknown cytogenetics

(because the cytogenetic test was unsuccessful) are within the range that NICE normally considers an acceptable use of NHS resources (see sections 3.23 and 3.24). Therefore, gemtuzumab ozogamicin can be recommended for these groups of people. Because no clinical- or cost-effectiveness analysis was presented for people whose disease has unfavourable cytogenetics, gemtuzumab ozogamicin cannot be recommended for this group (see section 3.25).

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 has acute myeloid leukaemia and the healthcare professional responsible for their care thinks that gemtuzumab ozogamicin is the right 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 C.

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.

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