Healthcare Improvement Scotland | SMC Advice on new medicines

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SMC2130

liposomal formulation of daunorubicin/cytarabine 44mg/100mg powder for concentrate for solution for infusion (Vyxeos®)

Jazz Pharmaceuticals UK Ltd

8 February 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and ultra-orphan medicine process

liposomal formulation of daunorubicin/cytarabine (Vyxeos®) is accepted for use within NHSScotland.

Indication under review: The treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (AML) or AML with myelodysplasia-related changes.In a randomised phase III study, in adults (aged 60 to 75 years) with high risk AML, liposomal daunorubicin/cytarabine improved overall survival when compared with a standard of care regimen.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of liposomal daunorubicin/cytarabine. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

The treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).[1]

Dosing Information

The recommended body surface area based dosing schedule of liposomal daunorubicin/cytarabine, administered intravenously over 90 minutes is:

Therapy	**Dosing schedule**
First induction	daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 on days 1, 3, and 5
Second induction	daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 on days 1 and 3
Consolidation cycles	daunorubicin 29mg/m^2 and cytarabine 65mg/m^2 on days 1 and 3

A subsequent course of induction may be administered in patients who do not show disease progression or unacceptable toxicity. The attainment of a normal-appearing bone marrow may require more than one induction course. Evaluation of the bone marrow following recovery from the previous course of induction therapy determines whether a further course of induction is required. Treatment should be continued as long as the patient continues to benefit or until disease progression up to maximum of two induction courses.

The first consolidation course should be administered 5 to 8 weeks after the start of the last induction.

Consolidation therapy is recommended for patients achieving remission who have recovered to absolute neutrophil count (ANC) >500/microlitre and the platelet count has recovered to greater than 50,000/microlitre in the absence of unacceptable toxicity. A subsequent course of consolidation may be administered in patients who do not show disease progression or unacceptable toxicity within the range of 5 to 8 weeks after the start of the first consolidation. Treatment should be continued as long as the patient continues to benefit or until disease progression, up to a maximum of 2 consolidation courses.

Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products. Liposomal daunorubicin/cytarabine has a different posology than daunorubicin injection and cytarabine injection and it must not be interchanged with other daunorubicin and/or cytarabine containing products.

See summary of product characteristics (SPC) for further information including dose modification for specific clinical circumstances.[1]

Product availability date

03 September 2018

Liposomal formulation of daunorubicin / cytarabine (Vyxeos®) has been designated an orphan medicine by the European Medicines Agency (EMA) for the treatment of AML. It also meets SMC end of life and ultra-orphan criteria.

Background

Vyxeos® is a liposomal formulation of a fixed combination of daunorubicin and cytarabine in a 1:5 molar ratio, which has been shown to maximise synergistic antitumour effects in AML. Daunorubicin and cytarabine inhibit DNA replication and have a prolonged plasma half-life when administered in a liposomal formulation. Vyxeos® delivers a synergistic combination of daunorubicin and cytarabine to leukaemia cells for a prolonged period of time.[1, 2]

Liposomal daunorubicin/cytarabine for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

AMLs are a heterogeneous group of haematopoietic stem cell disorders which are characterised by incomplete maturation of blood cells and decreased production of normal haematopoietic cells. The associated pancytopenia results in symptoms including fatigue, dyspnoea, infection and bleeding. Incidence increases with age (at least half of people diagnosed are over 65 years old), male sex and European descent.[3, 4 5] High risk (secondary) AML, which includes AML caused by previous treatment with chemotherapy or radiotherapy (therapy-related AML) and AML with myelodysplasia-related changes, is a biologically distinct subcategory of AML and accounts for a substantial proportion of patients with the disease.[6] Initial treatment is split into an induction phase, such as conventional daunorubicin plus cytarabine '3+10' chemotherapy or fludarabine, cytarabine, granulocyte-colony stimulating factors and idarubicin (FLAG-Ida) regimens, and a consolidation phase, indicated upon clinical and haematological remission. Choice of treatment is determined by the fitness of the patient to receive intensive induction chemotherapy; this includes a risk assessment of treatment-associated mortality, particularly in older patients, those with poorer performance status, or complicating co-morbidities. Patients in remission may be

suitable for HSCT, which is given with curative intent. Patients considered not suitable for intensive induction therapy are managed with palliative systemic treatment such as low-dose cytarabine, or entry into clinical trials, or with best supportive care.[3, 7] Midostaurin and gemtuzumab ozogamicin have recently been accepted for use by SMC in subgroups of patients with AML.

Treatment related AML and AML with myelodysplasia related changes are associated with poorer prognosis than with *de novo* AML. Clinical experts consulted by SMC highlighted unmet need due to poor outcomes with current chemotherapy. Patients with secondary AML have been reported to have a median overall survival between 6 and 14 months.[8] Liposomal daunorubicin/cytarabine is an EMA orphan and also meets SMC end of life and ultra-orphan criteria.

SMC patient group submissions described how AML is an aggressive form of leukaemia which is often diagnosed following emergency presentation. Patients with secondary AML have an extremely poor prognosis. Current therapies were described as being extremely toxic and frequently require prolonged inpatient admission. Patient groups outlined how in addition to the significant symptom burden, the emotional impact of diagnosis can affect the mental health of patients, with patients reporting anxiety or depressive feelings. Emotional stress also affects carers and family members. Patients with AML often have difficulty performing some activities of daily living and may have problems taking care of themselves. Work / education can also be affected with either reduction of hours or cessation altogether, with associated financial consequences.

Impact of new technology

Summary of evidence on comparative efficacy

The evidence to support the efficacy and safety of liposomal daunorubicin/cytarabine comes from Study 301, which was an open-label, randomised, multicentre, phase III study comparing liposomal daunorubicin/cytarabine with a conventional daunorubicin plus cytarabine '3+7' regimen. The study enrolled patients aged 60 to 75 years at the time of diagnosis of AML, which had to be in accordance with World Health Organisation (WHO) criteria[9], and required confirmation of therapy related AML, AML with a history of myelodysplasia (MDS), AML with a history of chronic myelomonocytic leukaemia (CMML) or *de novo* AML with karyotypic abnormalities characteristic of MDS. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, a cardiac ejection fraction ≥50%, and could have had prior treatment with hypomethylating agents, such as azacitidine or decitabine for MDS or CMML. [2, 10]

Patients were randomised equally to receive liposomal daunorubicin/cytarabine or a regimen of conventional daunorubicin plus cytarabine '3+7' as induction and consolidation chemotherapy, detailed in Table 1 below. Patients were stratified by age (60 to 69 years and 70 to 75 years) and AML type (therapy-related AML, AML with a history of MDS with and without prior hypomethylating agents, AML with a history of CMML, and *de novo* AML with MDS-related cytogenetic abnormalities).[2, 10] Patients could receive up to two cycles of induction chemotherapy to achieve complete remission (CR) or CR without complete neutrophil or platelet recovery (CRi) followed by up to two cycles of consolidation (post remission) therapy. The number of induction and consolidation cycles a patient received depended on their response to treatment, confirmed by bone marrow assessement.[2, 10]

Table 1: Details of Study 301 liposomal daunorubicin/cytarabine and '3+7' induction and consolidation cycles. [2, 10]

	Liposomal daunorubicin/cytarabine	**Conventional daunorubicin plus cytarabine '3+7'**
First induction	Liposomal daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 by 90 minute IV infusion on days 1, 3, and 5	daunorubicin 60mg/m^2 on days 1 to 3 with cytarabine 100mg/m^2/day administered by 7 day continuous IV infusion
Second induction cycle could be administered for patients if a day 14 bone marrow assessment did not show hypoplastic marrow		
Second induction	Liposomal daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 by 90 minute IV infusion on days 1 and 3	daunorubicin 60mg/m^2 on days 1 and 2 with cytarabine 100mg/m^2/day by 5 day continuous IV infusion
Consolidation treatment was administered to patients with CR or CRi after induction		
First consolidation	Liposomal daunorubicin 29mg/m^2 and cytarabine 65mg/m^2 by 90 minute IV infusion on days 1 and 3	daunorubicin 60mg/m^2 on days 1 and 2 with cytarabine 100mg/m^2/day by 5 day continuous IV infusion
Second consolidation		

IV=intravenous, CR=complete response, CRi=complete response and incomplete recovery

Performance of allogenic haematopoetic stem cell transplant (HSCT) was at the discretion of the treating clinician.[2, 10] The use of concomitant treatments such as prophylactic anti-microbials for patients with an absolute neutrophil count <0.5x10^9/L, transfusion support and growth factor were as per institutional protocol and according to American Society of Clinical Oncology criteria.[11]

The primary outcome was overall survival, described as the time from randomisation to death from any cause, and was analysed in the intention to treat population which included

all randomised patients. Patients not known to have died by the last follow-up were censored at the time point they were last known to be alive. [2, 10]

At the primary analysis, after a median follow-up of 20.7 months, death had occurred in 68% (104/153) of patients in the liposomal daunorubicin/cytarabine group and 85% (132/156) of patients in the '3+7' group. Median overall survival was 9.56 months and 5.95 months respectively, hazard ratio (HR) 0.69 (95% confidence interval [CI]: 0.52 to 0.90),[2, 11] p=0.005.[11] For the respective groups, Kaplan-Meier estimates of 1 year overall survival were 42% and 28% and of 2-year overall survival were 31% and 12%.[2]

Secondary outcomes included: complete response (which required bone marrow blasts <5%, absence of extramedullary disease, absence of blasts with Auer rods, neutrophils ≥1.0x10^9/L and platelets ≥100x10^9/L); complete response with incomplete recovery (criteria were similar to complete response except patients had neutrophil or platelet counts less than those required for a complete response at day 35 or later); event free survival (defined as the time from randomisation to the date of induction treatment failure, relapse from complete response or complete response with incomplete recovery or death from any cause, whichever came first); remission duration (time from achievement of a remission [CR or CRi] to relapse or death from any cause); stem cell transplant rate and morphologic leukaemia-free state (which required bone marrow blasts <5%, plus the absence of extramedullary disease and/or the absence of blasts with Auer rods). Living patients not known to have any of these events were censored on the date of last assessment. Important secondary outcomes are described in Table 2.

Table 2. Important secondary outcomes of Study 301.[1, 2, 6, 11]

	Liposomal daunorubicin/cytarabine (n=153)	**Conventional daunorubicin plus cytarabine '3+7' (n=156)**
Complete response[6]	37% (57/153)	26% (40/156)
	OR 1.69 (1.03 to 2.78), p=0.04	
Complete response plus complete response with incomplete recovery[6]	48% (73/153)	33% (52/156)
	OR 1.77 (1.11 to 2.81) p=0.016	
Median event free survival, months[11]	2.5	1.3
	HR 0.74, 95% CI 0.58 to 0.96, p=0.021	
Median remission duration, months[11]	6.9 (n=73)	6.1 (n=52)
	HR 0.77 (0.47 to 1.26) p=0.294	
Allogenic haematopoetic stem cell transplant[6]	34% (52/153)	25% (39/156)
	OR 1.54 (0.92 to 2.56) p=0.097	
Morphologic leukaemia-free state[6]	69% (87/126)	55% (66/156)
	OR 1.78 (1.05 to 3.03), p=0.017	

'3+7' = 3 days daunorubicin treatment and 7 days cytarabine treatment, HR=hazard ratio, CI=confidence interval, OR=Odds ratio.

An exploratory analysis of overall survival, landmarked at the point of receiving HSCT reported results consistent with the primary analysis: median overall survival had not been reached in the liposomal daunorubicin/cytarabine group and was 10.2 months in the '3+7' group (HR 0.46 [95% CI: 0.24 to 0.89]). Data from patients that proceeded to HSCT suggest that liposomal daunorubicin/cytarabine treatment prior to HSCT was not associated with an increase in transplant related mortality after HSCT.[11] The study did not assess patient reported outcomes.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The safety analysis set included all treated patients (liposomal daunorubicin/cytarabine n=153; '3+7' n=151). More patients treated with liposomal daunorubicin/cytarabine achieved a complete response and went on to receive consolidation cycles than those treated with the '3+7' regimen (32% versus 21%), which resulted in a longer median duration of overall treatment for patients in the liposomal daunorubicin/cytarabine group than in the '3+7' group, 62 days versus 41 days.[2] In the liposomal daunorubicin/cytarabine (n=153) and '3+7' (n=151) groups respectively, any grade of adverse event (AE) was reported for 100% of patients in both groups, related AEs in 95% in both groups, serious AEs occurred in 59% and 43%, discontinuation due to AE was 2.0% and 1.3% and death due to treatment related adverse events was recorded for 20% and 19% of patients. AEs occurring after HSCT were not counted.[2, 6, 12]

For the liposomal daunorubicin/cytarabine (n=153) and '3+7' (n=151) groups respectively, the most frequently reported treatment emergent AEs were febrile neutropenia (63% versus 60%), nausea (51% versus 53%), diarrhoea (46% versus 66%), constipation (43% versus 39%) and peripheral oedema (41% versus 43%).[6] The following AEs were also reported for the liposomal daunorubicin/cytarabine and '3+7' groups respectively within 30 days of the last dose, haemorrhage (74% versus 53%); rash (55% versus 36%); catheter/device/injection site reaction (16% versus 11%); and visual impairment (except bleeding) (12% versus 5%).[11]

Recovery from cytopenias may be delayed resulting in a higher incidence of low grade bleeding events and serious infections with liposomal daunorubicin/cytarabine than with '3+7' and liposomal daunorubicin/cytarabine administration includes an acute copper load with unknown risk.[6, 11]

Summary of clinical effectiveness issues

In the pivotal Study 301, the median overall survival was longer by 3.6 months, for patients treated with liposomal daunorubicin/cytarabine than with the conventional daunorubicin plus cytarabine '3+7' regimen, 9.56 months and 5.95 months respectively, HR 0.69 (95% CI: 0.52 to 0.90), p=0.005. Using Kaplan-Meier estimates, higher proportions of patients in the liposomal daunorubicin/cytarabine group were alive after 1 year (42% versus 28%) and 2 years (31% versus 12%) of treatment. There were also significant improvements in the secondary outcomes of event free survival and responses rates, and more liposomal daunorubicin/ cytarabine treated patients received HSCT. [2]

A higher proportion of patients in the liposomal daunorubicin/cytarabine group underwent HSCT than those treated with '3+7'; 34% versus 25%. Undergoing HSCT could increase survival. Treatment with liposomal daunorubicin/cytarabine resulted in more patients obtaining CR or Cri than '3+7' (48% versus 33%) and therefore increased the suitability of patients for transplant as would be expected for a more effective treatment. The decision to undergo HSCT was based on individual institutional criteria.[2]

Study 301 only included patients aged 60 to 75 years old. The European Medicines Agency advises that the biology of t-AML and AML-MRC are reasonably consistent across the adult population, so extrapolation of efficacy to patients with these disorders and outside this age range is appropriate.[6] The study had an open-label design given the significant differences in administration and visual properties of the medicines; this may have contributed to five patients randomised to the '3+7' regimen (n=156) withdrawing from the study prior to receiving study treatment. No patients randomised to treatment with liposomal daunorubicin/cytarabine withdrew from the study prior to receiving treatment. However the use of overall survival as the primary outcome is not open to bias.[2] Study 301 did not assess health-related quality of life.

There are some differences between the daunorubicin plus cytarabine '3+7' regimen in study 301 and the daunorubicin plus cytarabine '3+10' regimen most commonly used in Scottish practice, which may affect the generalisability8 of the study results. There is a lack of robust evidence to suggest a difference between these regimens in terms of efficacy. Clinical experts consulted by SMC considered that the FLAG-Ida regimen may also be a relevant comparator for this indication in some patients. The AML15 study which was conducted in patients with de novo or secondary AML, showed that FLAG-Ida is clinically comparable with daunorubicin plus cytarabine '3+10'. However, the majority of the patients in this study had a diagnosis of *de novo* AML, therefore comparative efficacy in patients with secondary AML (therapy-related AML or AML with myelodysplasia-related changes) is less certain. [14]

SMC recently accepted midostaurin and gemtuzumab ozogamicin for AML, which are both used in combination with a daunorubicin and cytarabine regimen. Neither of these medicines has been studied in combination with liposomal daunorubicin/cytarabine for safety or efficacy.

Clinical experts consulted by SMC considered that liposomal daunorubicin/cytarabine is a therapeutic advancement as it improved overall survival and remission rates in patients with a poor prognosis in the pivotal study, and that its place in therapy would be in accordance with the licensed indication.

Patient groups noted that liposomal daunorubicin/cytarabine provides an additional treatment option with improved outcomes compared with current treatments. Liposomal daunorubicin/cytarabine would offer an increased chance for patients to receive HSCT, which is a key benefit, as it represents the only curative option for patients. Patient groups noted there were potentially serious side-effects associated with both current intensive chemotherapy regimens and with liposomal daunorubicin/cytarabine.

Summary of patient and carer involvement

The following information reflects the views of the specified patient groups.

- We received patient group submissions from Leukaemia CARE and Bloodwise, both organisations are registered charities.
- Leukaemia CARE has received 12.6% pharmaceutical company funding in the past two years, with none from the submitting company. Bloodwise has received 0.9% pharmaceutical company funding in the past two years, including from the submitting company.
- AML is a rapidly progressing form of leukaemia with a significant symptom burden. The emotional impact of diagnosis can affect the mental health of patients and emotional stress also affects carers and family members. Patients with AML often have difficulty living independently which may be associated with financial consequences.
- Patients with secondary AML have an extremely poor prognosis. Current therapies are extremely toxic and frequently require prolonged inpatient admission.
- Liposomal daunorubicin/cytarabine provides an additional treatment option which improves the chance of remission, receiving a HSCT and increasing overall survival. Receiving a HSCT is a key benefit, as it represents the only curative option for these patients.
- Although liposomal daunorubicin/cytarabine is associated with serious adverse effects, these are similar to other chemotherapy options.

Value for money

The submitting company presented a cost-utility analysis which compared liposomal daunorubicin/cytarabine with conventional daunorubicin/cytarabine '3+7' regimen as induction chemotherapy in patients with untreated, high-risk (secondary) AML. The population in the economic analysis is based on Study 301, which enrolled patients 60 to 75 years of age. The sensitivity analysis explored including a younger population (age <60 years old) and a relative risk was applied to the probability of remission, progression and overall survival (OS) associated with the 60 to 69 years subgroup study data.

Treatment patterns in the analysis reflect Study 301 which followed North American guidelines as detailed by the National Comprehensive Cancer Network. AML patients enter the model with stable disease and receive either one or two rounds of induction therapy, after which they may achieve remission. Those who achieve remission may receive up to two rounds of consolidation (that is, 0, 1, or 2 rounds). Patients receiving 0, 1, or 2 rounds of consolidation may receive a transplant. Patients achieving remission post-induction may relapse after consolidation or transplantation. Patients who do not achieve remission post-induction may progress (receiving either non-intensive therapy, salvage therapy, or best supportive care) or receive a transplant. The model uses a survival-partition approach over a 30-year time horizon, with distinct survival curves for patient cohorts defined by their treatment pathway. For each cohort, the number of patients in each health state (event-free, progressed, and death) at each model cycle are calculated using the OS and event-free survival patient-level data from Study 301. Standard parametric fits were assigned to extrapolate these curves beyond the trial follow-up. Adverse events occurring with at least 5% frequency in Study 301 are also included in the model.

Patient quality of life is tracked over the analysis time horizon. Patients derive health utilities according to their AML state and incur disutilities associated with the treatment received (induction/consolidation/transplant) and the treatment setting (inpatient/outpatient). The utility values used in the model were derived from an in-house vignette-based study in a general population sample.

The model includes medicine acquisition and administration costs for liposomal daunorubicin/ cytarabine, '3+7' regimen, and other medicines used in non-intensive and salvage therapy, considering the treatment regimen and dosage size. Other costs include transplant costs, monitoring costs, and AEs costs. It is assumed 50% of liposomal daunorubicin/cytarabine consolidation infusions are being carried out in an outpatient setting, while 100% of the '2+5' consolidation regimen infusions (associated with '3+10' induction) are inpatient.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland.

In the base case analysis the company estimated an incremental cost-effectiveness ratio (ICER) of £24,314 based on a quality-adjusted life-year (QALY) gain of 1.31. The majority of life years and associated QALYs gained is achieved in the post-transplant remission state of the model. Table 3 presents selected key parameters and scenarios to which the ICER was most sensitive in the deterministic analysis.

Table 3: Deterministic sensitivity analysis results

Analysis	Parameter	ICER
1	Alternative fit for liposomal daunorubicin/ cytarabine post-HSCT OS – log-normal	£38,635
2	Probability of achieving post-induction response – no treatment effect	£25,092
3	Post-HSCT survival assumed to be 1.34 SMR	£26,649
4	Responders post-HSCT do not remain relapse-free	£39,450
5	Utilities of health states reduced by 20%	£26,867
6	Time horizon - 5 years	£64,782
7	Time horizon - 10 years	£37,011
8	Time horizon - 15 years	£29,047
9	'3+10' dosing from UK guidelines	£19,269
10	30% of patients age < 60 years	£19,429
11	20% of patients age < 60 years and no age effect on response rate	£22,347
12	Scenario analysis to reflect Scottish treatment regimens; responders post-transplant allowed to relapse; 1.34 SMR for post-HSCT mortality	£35,603
13	Assume 100% liposomal daunorubicin/ cytarabine consolidation delivered in inpatient setting	£27,354
14	Alternative utility values using UK study which assumes equal disutility for both treatments	£27,709

OS, overall survival; SMR, standardised mortality ratio; HSCT, haematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio

Several uncertainties and limitations relating to the economic case presented were identified:

- The base case analysis assumes HSCT is a cure as patients responding to treatment and receiving a HSCT remain in remission throughout the time horizon of the analysis and their mortality risk is referenced to the general population. SMC clinical experts suggest a relapse rate post-HSCT of around 30% and a long-term mortality rate of around 50%. When the base case assumption is relaxed the ICER increases (analysis 3 and 4).

- Health utility scores were derived from a vignette-based time-trade-off study using a general population sample. No mapping onto EQ-5D was attempted and preference for health states was elicited by individuals not having the disease, hence limiting comparability with other interventions and across other disease areas. When alternative utilities from published studies where no difference in disutility between treatments is assumed, the ICER increases (analysis 13).
- The majority of life years and associated QALY gains are derived in the post-transplant remission state of the model through extrapolation of OS. The extrapolation is based on patient-level data from a small number of patients in the study which are heavily censored towards the end of the follow-up. Hence the extrapolation is subject to uncertainty and the ICER seems to be sensitive to the choice of parametric model for extrapolating OS (analysis 1), but also to shorter time horizons (analysis 6-8). Using a shorter time horizon also seems more plausible in the context of an end-of-life treatment.
- The '3+7' induction regimen used in the analysis as the comparator differs slightly from the '3+10' regimen used in Scottish practice, but the general consensus among clinical experts is that no major differences in clinical efficacy are expected between these two regimens. An alternative scenario using '3+10' dosing from UK guidelines was provided (analysis 9), the decrease in the ICER being mainly driven by a considerably lower number of days in hospital, with liposomal daunorubicin/cytarabine., FLAG-Ida is another relevant comparator used in Scotland according to clinical experts, particularly in fitter patients, but was not included in the economic analysis. Further evidence from the AML15 study shows that FLAG-Ida is clinically comparable with 3+10, but associated with increased resource use. However, as described above, the majority of patients in this study had de novo AML.
- The model population does not reflect the full licensed indication which has no age restriction. The model did explore the impact of a younger population (<60, 56.5 mean age) with the clinical effects in this population extrapolated from the 60 to 69 study population with some adjustments. These adjustments are subject to uncertainty and seem to imply the relative effectiveness of liposomal daunorubicin/cytarabine against the '3+7' regimen in terms of OS is higher in the younger population than it is in the reference study population (analysis 10). This is not supported by study data as a comparison of age stratified study data (60 to 69 versus 70 to 75) suggests an opposite effect of age on OS. Analysis 11 above which assumes the same response rate as observed in the study population provides a more appropriate estimate of the impact on the ICER of including a proportion of patients aged < 60 years.

Impact beyond direct health benefits and on specialist services

Liposomal daunorubicin/cytarabine is administered as a 90 minute intravenous infusion on 2 or 3 separate days compared with the '3+10' regimen which includes a twice daily infusion of cytarabine over 10 or 8 days. This is expected to translate to shorter and fewer inpatient stays. Improving patient wellbeing through disease remission or reducing time in hospital would have a positive impact on the patient's family and carers. It may allow a return to normal every day routine and reduce the emotional, physical and financial burden on families and carers.

Costs to NHS and Personal Social Services

The submitting company estimated there would be 19 patients eligible for treatment with liposomal daunorubicin/cytarabine per year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

Conclusion

The Committee also considered the benefits of liposomal daunorubicin/cytarabine in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the following criteria were satisfied: a substantial improvement in life expectancy and the potential to bridge to a definitive therapy. In addition, as liposomal daunorubicin/cytarabine is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and application of the appropriate SMC modifiers, the Committee accepted liposomal daunorubicin/cytarabine for use in NHSScotland.

Additional information: guidelines and protocols

The European LeukemiaNet consensus guidance "Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel" was published in November 2016.[7] Standard intensive induction chemotherapy is recommended to comprise seven days of cytarabine continuous infusion (100 to 200 mg/m^2) and three days of

anthracycline (eg daunorubicin 60mg/m^2). Consolidation therapy recommended in the guidance include allogeneic SCT (adverse or intermediate risk genetics), or between two and four cycles of intermediate dose cytarabine.[7]

The European Society for Medical Oncology (ESMO) published guidance entitled "Acute myeloblastic leukaemias in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in August 2013.[4] The ESMO guidance recommends that "induction chemotherapy should include an anthracycline and cytarabine with the particularly well-known and time-honoured '3+7' regimen…Consolidation therapy in AML is warranted once patients have reached clinical and haematological remission. There is no consensus on a single 'best' post-remission treatment."[4]

The British Committee for Standards in Haematology (BCSH) published Guidelines on the management of acute myeloid leukaemia in adults in 2006.[13] This guidance has been archived.

These guidelines predate the licensing of liposomal daunorubicin/cytarabine.

Additional information: comparators

Conventional daunorubicin plus cytarabine regimen and fludarabine, cytarabine, granulocyte-colony stimulating factors and idarubicin (FLAG-Ida) regimen.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
Liposomal daunorubicin/ cytarabine	**Induction** **Cycle 1** **daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 IV infusion on days 1, 3, and 5**	**27,486**
	Cycle 2 **daunorubicin 44mg/m^2 and cytarabine 100mg/m^2 IV infusion on days 1 and 3**	**18,324**

	Consolidation **daunorubicin 29mg/m^2 and cytarabine 65mg/m^2 IV infusion on days 1 and 3**	**18,324**
Daunorubicin Cytarabine '3+10'	Induction Cycle 1 daunorubicin 60mg/m^2 IV infusion on days 1 to 3 cytarabine 100mg/m^2 IV infusion twice daily on days 1 to 10	1,334
	Cycle 2 daunorubicin 50mg/m^2 IV infusion on days 1 to 3 cytarabine 100mg/m^2 IV infusion twice daily on days 1 to 8	1,106
	Consolidation Patients <60 years old cytarabine 3g/m^2 IV infusion twice daily on days 1, 3 and 5	1,185
	Patients ≥60years old cytarabine 1.5g/m^2 IV infusion twice daily on days 1, 3 and 5	593
FLAG-Ida	Induction Cycle 1 and 2 fludarabine 30mg/m^2 IV infusion on days 1 to 5 cytarabine 2,000mg/m^2 (<60 years) or 1,000mg/m^2 (≥60 years) IV infusion on days 1 to 5 filgrastim 300 micrograms s/c once daily for 7 days Idarubicin 8mg/m^2 IV infusion daily on days 3, 4 and 5	2,961 to 3,320

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online on 02 November 2018 (Vyxeos®) and BNF online on 02 November 2018 (cytarabine and daunorubicin). Costs calculated using assuming a body surface area of 1.8m^2 and the full cost

of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 17 December 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal*: http://www.scottishmedicines.org.uk/About_SMC/Policy

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.