Evaluation of the cost-effectiveness of dexrazoxane for the prevention of anthracycline-related cardiotoxicity in children with sarcoma and haematologic malignancies: a European perspective

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Abstract
Background: Anthracycline-treated childhood cancer survivors are at higher risk of cardiotoxicity, especially with cumulative doses received above 250 mg/m². Dexrazoxane is the only option recommended for cardiotoxicity prevention in high-risk patients supported by randomised trials but its cost-effectiveness in paediatric cancer patients has not been established.

Methods: A cost-effectiveness model applicable to different national healthcare system perspectives, which simulates 10,000 patients with either sarcoma or haematologic malignancies, based upon baseline characteristics including gender, age at diagnosis, cumulative anthracycline dose and exposure to chest irradiation. Risk equations for developing congestive heart failure and death from recurrence of the original cancer, secondary malignant neoplasms, cardiac death, pulmonary death, and death from other causes were derived from published literature. These are applied to the individual simulated patients and time until development of these events was determined. The treatment effect of dexrazoxane on the risk of CHF or death was based upon a meta-analysis of randomised and non-randomised dexrazoxane studies in each tumour type. The model includes country specific data for drug and administration costs, all aspects of heart failure diagnosis and management, and death due to different causes for each of the five countries considered; France, Germany, the UK, Italy, and Spain.

Results: Dexrazoxane treatment resulted in a mean QALY benefit across the five countries ranging from 0.530 to 0.683 per dexrazoxane-treated patient. Dexrazoxane was cost-effective for paediatric patients receiving anthracycline treatment for sarcoma and for haematologic malignancies, irrespective of the cumulative anthracycline dose received. The Incremental Cost Effectiveness Ratio (ICER) was favourable in all countries irrespective of anthracycline dose for both sarcoma and haematological malignancies (range: dominant to €2196). Individual ICER varied considerably according to country with dominance demonstrated for dexrazoxane in Spain and Italy and ratios approximately double the European average in the UK and Germany.
Background
Anti-cancer treatments, such as anthracycline therapy and radiation therapy, are used widely in the treatment of childhood cancer, particularly in a wide spectrum of solid organ and haematologic malignancies including leukaemia, lymphoma and sarcomas. Approximately 50–60% of childhood cancer survivors have been treated with an anthracycline regimen [1]. These treatments have several late adverse effects, with cardiotoxicity being one of the most widely recognised [2, 3].

Cardiotoxicity caused by anthracycline therapy manifests along a continuum from asymptomatic left ventricular dysfunction (ALVD) (a surrogate measure of anthracycline-induced cardiotoxicity) to congestive heart failure (CHF) [4]. Cumulative anthracycline dose is an independent risk factor for CHF, with higher cumulative doses, especially > 250 mg/m², leading to higher risk of cardiotoxicity [5]. However, even at lower doses, subclinical cardiotoxicity may be observed, and lower doses may compromise efficacy [6]. Children with sarcomas are frequently treated with some of the highest cumulative anthracycline doses, making them particularly vulnerable to cardiac injury [7, 8].

In developed countries, total expenditure on CHF ranges between 1 and 2% of the total healthcare budget, with medical costs increasing with extent of left ventricular systolic dysfunction and the severity of the disease [9]. Direct medical costs include those associated with initial investigations and with treatment.

Intravenous dexrazoxane is currently the only agent recommended for cardiotoxicity prevention in high-risk patients [10]. Until recently, dexrazoxane use was restricted to adults with advanced or metastatic breast cancer who had already received at least 300 mg/m² of doxorubicin or equivalent cumulative dose of another anthracycline. In its 2017 update to the European SmPC, the EMA noted that there is no evidence to support previous concerns about an increased incidence of second malignant neoplasm (SMN) in patients who have received dexrazoxane and modified the contraindication, limiting its administration to paediatric patients planned to receive > 300 mg/m² of doxorubicin or equivalent cumulative dose of another anthracycline. Follow up results among 1022 patients from the Children’s Oncology Group (COG) AAML0531 study strongly indicate that the occurrence of left ventricular dysfunction whilst receiving cancer treatment was associated with poorer oncologic treatment outcomes [11].

The cost-effectiveness of dexrazoxane in paediatric cancer survivors is yet to be established. Here we present a cost-effectiveness model, based on European-wide healthcare data and costs, that aims to assess the budget impact and cost-effectiveness of dexrazoxane in children with sarcoma or haematologic malignancies.

Materials and methods
Model design
A cost-effectiveness model applicable to different national healthcare system perspectives across Europe was developed. This model was populated with data for France, Spain, Italy, Germany, and the United Kingdom (UK).

The model simulated children and adolescent patients with either sarcomas or various haematologic malignancies (including acute myeloid leukaemia, acute lymphoblastic leukaemia, Hodgkin lymphoma and non-Hodgkin lymphoma) who survived for 5 years after diagnosis and who received treatment with chemotherapy regimens containing an anthracycline, such as doxorubicin or epirubicin. Each patient had a set of baseline characteristics including sex, tumour type, age at cancer diagnosis, cumulative anthracycline dose, and exposure to chest irradiation (Fig. 1). The baseline parameters were based on data from Cancer Research UK [12].

The same national cohorts entered two treatment arms in the model: patients having received dexrazoxane versus those who had not. Three different dose thresholds for anthracycline exposure were employed in the model to allow for different treatment paradigms and clinical eventualities (exposure to any dose of anthracycline, > 250 mg/m², and > 100 mg/m²). These thresholds were also chosen in order to determine the cost-effectiveness of dexrazoxane when initiated at the start of anthracycline therapy or after prolonged treatment with a higher anthracycline dose.

A targeted literature review was conducted in May 2018 to identify clinical information and economic evidence describing healthcare resource use, costs, and...
quality of life (QoL) utility values associated with anthra-
cycline administration and the management of cardiac
failure in each of the five countries addressed by the
model. This literature review also sought to identify risk
equations to link surrogate outcomes to patient out-
comes, such as heart failure and other cardiac events.
Finally, the review identified all published clinical trials
evaluating the addition of dexrazoxane to anthracycline
therapy in the treatment of childhood cancer (see Addi-
tional file 1). To maximise the volume of outcomes data
that could be included in the model, the search strategy
included studies where dexrazoxane was administered at
10:1 to doxorubicin (the current recommended ratio) or
at 20:1 to doxorubicin (the historical regimen).

Several patient subgroups were considered in the
model based on additional parameters known to affect
lifetime risk of cardiotoxicity, for example age at treat-
ment initiation, gender, or chest irradiation.

The model was programmed with a base case setting
using the most robust, conservative data plus other pro-
grammed scenario analyses, such as one of three anthra-
cycline administration dose ranges (any anthracycline
dose; > 250 mg/m²; and > 100 mg/m²), to allow the user to
select alternative data sources for the key clinical events
in the model.

Clinical inputs
Known risk equations from the published literature
were applied to the individual simulated patients. Baseline risk of developing CHF was based upon risk
equations and cumulative incidence graphs presented
in the standard risk model developed by Chow et al.
[13], as it best matched the available input variables
from dexrazoxane studies, in which data from the US
Childhood Cancer Survivor Study (CCSS) was used to
predict heart failure in survivors of childhood cancer
where clinical dose information was known [3, 14].
For the purpose of this base case analysis, the chance
of an individual patient receiving chest irradiation was
set at 18%, based on the incidence of chest irradiation
reported in a large retrospective study of dexrazoxane
in children with anthracycline-induced cardiotoxic-
ity [15]. An alternative risk model for CHF was devel-
oped for the sensitivity analysis, based on the results
of a retrospective analysis of cardiac outcomes in adult
survivors of the CCSS cohort [16]. This model included
the impact of anthracycline dose, age at diagnosis, and
gender on the risk of CHF, but, unlike that of Chow,
only included two anthracycline dose categories and
did not account for chest radiation. The risk of devel-
oping ALVD was estimated at three times greater than
the risk of developing CHF [17–19], calculated accord-
ing to age. Polynomial extrapolation of the cumulative
CHF incidence was used for the base case, whereas lin-
ear extrapolation was used for the sensitivity analysis
(Table 1).

Risk of death calculations included: death from recur-
rence or progression of the original cancer, developing a
secondary malignancy, cardiac death, pulmonary death,
death from external causes (accidents and violence),
and death from other causes including infection, other
diseases, and unknown cause. Risk of death by different
causes was modelled using cause-specific cumulative
mortality curves in the CCSS and sex-matched US pop-
ulation produced by Mertens et al. (see Fig. 2a and b)
[20]. For the sensitivity analysis, the risk of death from
different causes was modelled using national life tables
for death, by age and gender [24], and distribution by
cause of death for 5-year survivors of childhood cancer
in France and the UK, as reported by Tukenova et al.
[21]. A standardised mortality ratio (SMR) for child-
hood cancer survivors versus the general population

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**Fig. 1** Model schematic. AC, anthracycline; ALVD, asymptomatic left ventricular disease; CHF, congestive heart failure; XRT, chest irradiation

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Table 1

| Cause of Death | Risk Calculation Method |
|----------------|-------------------------|
| Death from recurrence or progression of the original cancer |
| Developing a secondary malignancy |
| Cardiac death |
| Pulmonary death |
| Death from external causes (accidents and violence) |
| Death from other causes including infection, other diseases, and unknown cause |
was applied, based on findings that patients have a higher risk of cardiac mortality if they have ALVD or CHF [25].

In the current model, the treatment effect of dexrazoxane was based on relative risks from a published meta-analysis of randomised and non-randomised dexrazoxane studies of sarcoma and haematological malignancies, which evaluated the impact of adding dexrazoxane to anthracycline-based chemotherapy on the incidence of ‘clinical’ cardiotoxicity (CHF) and ‘clinical plus sub-clinical’ (ALVD) cardiotoxicity [26]. The Mantel–Haenszel (M–H) method was used to calculate the treatment effect of dexrazoxane in the base case, and the Bayesian approach was used in the sensitivity analyses (see Additional file 2).

Cost inputs
The model programmed each patient’s treatment pathway and summed all costs and benefits accrued over the patient’s lifetime. Time spent in each health state (healthy, with ALVD, or with CHF), costs and utilities assigned to each health state, and total costs and outcomes were calculated.

The following cost parameters were included: drug and administration costs of dexrazoxane therapy; costs of heart failure diagnosis; heart failure treatment and management; heart failure hospitalisation; cardiac death; death from cancer; and death from other causes. National costs data were accessed from publicly available sources (see Additional files 3 and 4); where individual national healthcare costs systems did not match the model structure precisely, e.g. Diagnosis-Related Groups (DRG) costs in Germany, the model was either adapted to allow for the difference or approximations, based upon the available data, were made to allow for the design discrepancies (see Additional file 4). Where relevant, costs and benefits were discounted by 3.5% per annum, which is the standard reference rate in many European countries [27].

Utility data, differentiated by age and health state (healthy, with ALVD, or with CHF), were included in the model to enable the conversion of life years to quality-adjusted life years (QALYs) (see Additional file 5) [22]. In the sensitivity analyses, utility values were based on the New York Heart Association classes I and III, [0.855 (0.845; 0.846) and 0.673 (0.665; 0.690)] representing health states ALVD and CHF respectively [23].

Model analyses
The primary outcome of the model was an estimation of total costs and benefits per patient, and the incremental costs and benefits incurred when receiving dexrazoxane. The incremental cost-effectiveness ratio (ICER) for using dexrazoxane was calculated.

Secondary outcomes of the model included the number of patients developing ALVD, the number of patients developing CHF, and the proportion of patients dying from either recurrence of the original cancer, cardiac illness, pulmonary reasons, or other causes.

Sensitivity analyses were undertaken using different data sources and predictive approaches for long-term outcomes (e.g. risk of developing CHF) as indicated in Table 1.

Results
Meta-analysis results
Five non-randomised studies, and one randomised study, of dexrazoxane in paediatric patients with sarcoma were identified from the literature [28–33]. These studies comprised 126 patients who received dexrazoxane and 154 patients in comparator groups. A further five paediatric studies (three randomised and two non-randomised studies) were identified involving a total of 606 patients with haematological malignancies who
received dexrazoxane and 536 patients in the comparator groups [15, 33–37]. In these studies, acute lymphoblastic leukaemia and non-Hodgkin lymphoma were the most prevalent cancer types. Two further non-randomised studies reported outcomes data combining patients who had received anthracycline treatment for either sarcoma or haematological malignancy [38, 39]. Outcomes for the 176 patients who had received dexrazoxane and the 190 patients in the comparator group in these two studies were included in the meta-analysis for each tumour type.

The results of the meta-analyses were similar irrespective of the approach used (M–H or Bayesian). For patients with haematological malignancies, the relative risk (RR) of a cardiovascular event after dexrazoxane treatment compared to controls was 0.137 (95% confidence interval [CI] 0.032 to 0.582) when estimated using the M–H approach and 0.107 (95% CI 0.026 to 0.444) using the Bayesian approach. The

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**Fig. 2 a, b** Survival curves for paediatric patients who have not been treated with dexrazoxane who a have CHF, by age at diagnosis, and b are cancer survivors, conditional on surviving until the age at cancer diagnosis, compared to survival among the general population.
equivalent RR for patients receiving anthracycline treatment for sarcoma were 0.188 (95% CI 0.072 to 0.494) and 0.219 (95% CI 0.086 to 0.558), respectively. Tests for the homogeneity of RR were not statistically significant for either tumour indication, demonstrating that the results are valid. The results presented are those calculated using the M–H approach for RR, model results for the Bayesian RR outcomes are included in Additional file 2.

Model results

The additional duration of lifespan conferred by dexrazoxane treatment was small, amounting to approximately 0.02 life years per treated patient, irrespective of anthracycline dose administered or underlying indication for treatment. Dexrazoxane treatment resulted in a mean QALY benefit across the five countries ranging from 0.530 to 0.683 per dexrazoxane-treated patient. Dexrazoxane treatment conferred increasing benefits in terms of QALYs according to the total dose of anthracycline received with a mean of 0.530 QALY across all five countries for sarcoma patients receiving any anthracycline dose increasing to a mean of 0.596 QALY for sarcoma patients who received more than 250 mg/m² anthracycline. The mean QALY gains for patients with haematological malignancies were 0.592 and 0.683, respectively. Model outcomes for lifespan and QALY were similar across all five countries, likely reflecting broadly comparable overall health outcomes and survival in each setting. Example results for the base case for France for all anthracycline doses are presented in Table 2. Results for all countries and anthracycline doses included in the analysis can be seen in Additional file 6.

Overall, healthcare costs increased with increasing anthracycline dose, however, the additional costs due to...
dexrazoxane administration were offset at least in part by reductions in costs associated with cardiac failure and death. In two countries, Italy and Spain, these savings exceeded the acquisition cost of dexrazoxane by (£70–110) according to the dose of anthracycline administered. The highest additional costs of treatment due to dexrazoxane administration were in the UK at approximately £1464 (£1273) for sarcoma patients receiving >250 mg/m² doxorubicin or £1210 (£1052) if any total dose of doxorubicin was considered; costs for patients with haematological malignancies were slightly lower at £1281 and €1083, respectively.

The ICER for dexrazoxane treatment was favourable in all countries irrespective of anthracycline dose for both sarcoma and haematological malignancies. Given the differences in healthcare costs across different healthcare systems, the ICER varied marginally between countries (range: dominant to €2196) with the highest ICER reported in Germany and the UK with lowest in Spain and Italy (see Table 3 and Additional file 6). Interestingly, the ICER increased with anthracycline dose for both patients with sarcoma and patients with haematological malignancies.

### Table 3 ICER for dexrazoxane administration according to anthracycline dose treatment of sarcoma and haematological malignancies

| Malignancy type | France (£) | Germany (£) | UK (£) | Italy (£) | Spain (£) |
|-----------------|------------|-------------|--------|-----------|----------|
| Sarcoma         |            |             |        |           |          |
| All AC doses    | 895        | 2006        | 1983   | Dominant  | Dominant |
| > 100 mg/m²     | 891        | 1991        | 1986   | Dominant  | Dominant |
| > 250 mg/m²     | 982        | 2196        | 2135   | Dominant  | Dominant |
| Haematological  |            |             |        |           |          |
| All AC doses    | 559        | 1418        | 1590   | Dominant  | Dominant |
| > 100 mg/m²     | 563        | 1400        | 1579   | Dominant  | Dominant |
| > 250 mg/m²     | 586        | 1462        | 1630   | Dominant  | Dominant |

* £ sterling amounts converted to Euro at a rate of 1.15€ to one £ for calculations of mean values
* AC anthracyline, ICER incremental cost effectiveness ratio

indicated in Table 1 produced similar results to those reported for the base case above. The results for the one-way sensitivity analyses for France (example case) are presented in Table 4.

### Discussion

The results presented here indicate that dexrazoxane is a highly cost-effective therapy for the prevention of anthracycline cardiotoxicity in paediatric cancer patients. Few pharmacologic interventions offer such favourable ICER in the field of oncology and these results highlight the need for cardiologists and paediatric oncologists to take a multidisciplinary approach to optimise patient care in the face of cost-effective treatment options.

The highest anthracycline dose category in this model was arbitrarily set at >250 mg/m² since this reflected dose sub-group analyses in the clinical studies upon which the model is based. The results of the model can be anticipated to reflect expected outcomes in patients receiving >300 mg/m² anthracycline since the differences in model outcomes between anthracycline dose category are relatively small. Indeed, the model supports the use of dexrazoxane as recommended when the expected dose to be administered exceeds the 300 mg/m² anthracycline threshold as it demonstrates cost effectiveness irrespective of the actual anthracycline dose administered.

Current management of haematological malignancies in childhood typically involves administration of anthracycline doses as high as 250 mg/m². However, most recommended regimens limit anthracycline exposure to around 100 mg/m². Doses exceeding 250 mg/m² are often used for acute myeloid leukaemia and lymphomas [40]. Our core model only considered doses above 100 mg/m² since the lifetime risk of cardiotoxicity is much lower below it. Extrapolation of the results at higher dose levels and the results for all doses of anthracyclines suggest dexrazoxane treatment is likely to be cost-effective at lower anthracycline doses but this needs to be considered in the light of limited efficacy and safety data for the >250 mg/m² dose level.

This model relies upon the assumption that differences in the proportions of patients observed to have left ventricular dysfunction based upon arbitrary echocardiographic outcomes during anthracycline treatment will translate into differences in long term cardiac outcomes. This hypothesis cannot be tested but it is supported by long term observational data amongst patients treated with dexrazoxane or placebo in COG trials [41]. At a mean of 16 years after initial diagnosis, dexrazoxane-treated patients had significantly higher left ventricular ejection fraction overall compared with controls (those who did not receive dexrazoxane), with significantly higher myocardial wall stress and dysfunction reported in the subset
of patients from one study (COG P9404) who had received 360 mg/m² of doxorubicin. An additional weakness of this model is the inclusion of studies where dexrazoxane was administered at a dose of 20:1 the doxorubicin dose in the meta-analyses of treatment effect. Whilst a 20:1 dose regimen was considered to have poorer safety profile than the 10:1 regimen, leading to its withdrawal, there are little data available to suggest it was significantly more efficacious. Therefore, for the purposes of constructing this model the advantages of including the additional volume of efficacy data were considered to outweigh the disadvantages of potential variations in cardioprotective benefit. Importantly, these modelled analyses assume no impact of dexrazoxane upon the incidence of SMN, nor do they include any allowance for improved oncologic outcomes that might be a consequence of dexrazoxane administration.

Although this model attempts to characterise the costs associated for each of the five countries reported, comparisons across countries should be treated with caution. Individual country data for the costs of investigations, and scope of costs related to in-patient and out-patient management were accessed from local sources. However, because there are differences in the way healthcare costs are calculated within each system, especially for those associated with the inpatient management of heart failure, comparisons are not on a fully like for like basis. This may explain in part the higher ICER reported for Germany and the UK but differences in medications acquisition costs are also relevant.

Conclusions
In conclusion, dexrazoxane is a highly cost-effective treatment for prevention of anthracycline related cardiotoxicity in paediatric patients with sarcoma and haematological malignancies. In two countries, Spain and Italy, the model demonstrates dominance for dexrazoxane in terms of ICER, whilst in the remaining three major European countries all model outcomes demonstrate an ICER less than one tenth of the recognised standard threshold for cost-effectiveness of £20,000–£30,000 set by NICE [42]. There should therefore be no economic barrier to the use of dexrazoxane for the prevention of anthracycline related cardiotoxicity in paediatric patients with sarcoma and haematological malignancies in Europe.

Supplementary information
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Authors’ contributions

SD developed the concept for the analysis and programmed the health economic model. JS reviewed and advised upon the different treatment populations considered in the model. EN adapted the model to different countries. JS and EN collated the data inputs for the model, statistical support was provided by KC. All authors reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This meta-analysis study is exempt from ethics approval as the study authors have collected and analysed data from previous clinical trials in which ethics approval and consent have already been obtained by the trial investigators. All data presented in this analysis are anonymous.

Consent for publication

This meta-analysis study involves the collection and analysis of published data presented in this analysis are anonymised.

Consenting to publication

This meta-analysis study involves the collection and analysis of published data from previous clinical trials, in which consent for publication has already been obtained by the trial investigators.

Competing interests

JS is an employee of Prism Ideas Ltd who received a grant from Clinigen Group PLC to support the development of the HE model. KC is an independent consultant who received fees from Prism Ideas in relation to the conduct of meta-analyses. SD is an employee of SHE Consulting and was a consultant to Prism Ideas regarding the development of the HE model.

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