Doxorubicin cardiotoxicity: prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiography in the current era

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of left ventricular ejection fraction (LVEF) monitoring to identify cardiotoxicity (e.g. congestive heart failure, CHF), developing during the course of doxorubicin (DOX) therapy, a commonly used chemotherapeutic agent in cancer patients, was examined. The diagnostic approach used for LVEF monitoring was equilibrium radionuclide angiocardiography (ERNA).

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients diagnosed with cancer who were receiving DOX-containing chemotherapy.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
Some effectiveness and resource use data were gathered from January 1993 to July 1997. The costs came from studies published from 1994 to 1998. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study and authors’ assumptions.

Link between effectiveness and cost data
The costing was, in part, carried out retrospectively on the same sample of patients as that used in the clinical study.

Study sample
Power calculations were not reported. A sample of consecutive patients diagnosed with cancer who had undergone two or more ERNA studies was identified from the database of Yale-New Haven Hospital Cardiovascular Nuclear Imaging Laboratory. Of the 411 patients initially identified, those who had received DOX in the past, those who received anthracycline agents other than DOX or a non-DOX-containing chemotherapeutic combination, and those who received a non-standard formulation of DOX (such as hepatic artery infusion of DOX) were excluded from analysis. Also excluded were patients with pre-existing CHF. The remaining 284 patients were eligible for follow-up. However,
adequate follow-up information could not be obtained in 19 patients. Thus, the final study sample comprised 265 patients who were monitored before and after DOX chemotherapy. These patients had a mean age of 53 (+/- 14) years and 76% were women.

Study design
This was a case series of patients who were followed at a single centre, the Yale-New Haven Hospital Cardiovascular Nuclear Imaging Laboratory. The patients were followed by chart review and/or by directly contacting the patient, their families and the patients' treating physicians. The average follow-up was 679 (+/- 426) days. Nineteen patients were lost to the follow-up assessment.

Analysis of effectiveness
The analysis of the clinical study was restricted to patients with complete follow-up data. The outcome measure used in the effectiveness study was the proportion of patients developing CHF. This was defined as the presence of symptoms of shortness of breath at rest or with physical activity in the absence of other factors contributing to these symptoms, as well as physical signs consistent with the diagnosis of CHF (New York Heart Association class II-IV). The numbers of possibly cardiac-related deaths and DOX discontinuations were also reported. On the basis of prior published experience, a population "at-risk" for CHF was defined as patients whose baseline LVEF was 50% or greater when they manifested a 10% or greater point fall in LVEF to a final LVEF of less than 50%, according to established guidelines.

Effectiveness results
Among those patients who were monitored, seven (2.6%) developed CHF, three of whom required hospital admission. The number of possibly cardiac-related deaths was 1 of a total of 90 deaths. Statistical differences between the patients who developed CHF and those in whom it did not were observed for several variables. In particular, diabetes mellitus (29% versus 4%; p=0.04), final cumulative dose of DOX (400 +/- 214 mg/m2 versus 284 +/- 107 mg/m2; p=0.007), the lowest LVEF encountered during the follow-up period (28% +/- 8% versus 55% +/- 8%; p<0.0001), concomitant use of 5-fluorouracil (71% versus 18%; p<0.004) and mediastinal irradiation (43% versus 12%; p=0.04).

A group of 41 patients were defined as "at-risk", while the remaining 224 patients were considered in the "low-risk" group. There were differences in the frequency of early discontinuation of DOX therapy (49% versus 6%; p<0.0001), overt CHF (12% versus 1%; p<0.0001), cancer-related deaths (59% versus 29%; p=0.0003), number of ERNA procedures (3.9 +/- 1.5 versus 3.2 +/- 1.3; p=0.002), baseline LVEF (58% +/- 8% versus 64% +/- 8%; p<0.0001), and the lowest LVEF during the follow-up (42% +/- 8% versus 57% +/- 7%; p<0.0001) in "at-risk" patients compared with the remaining patients, despite similar cumulative DOX dose.

DOX therapy was discontinued early in 34 patients during sequential LVEF monitoring. This was because of the appearance of criteria for DOX cardiotoxicity in the absence of any overt signs of CHF (20 patients; 59%), the appearance of overt CHF (2 patients), and a lack of therapeutic response (12 patients).

Clinical conclusions
The effectiveness evidence showed the clinical outcomes associated with patients who underwent ERNA studies.

Methods used to derive estimates of effectiveness
The authors made a key assumption on the efficacy of the comparator. The choice of the assumption was justified on the basis of some published information.

Estimates of effectiveness and key assumptions
It was assumed that 50% of patients in the "at-risk" population would have developed overt CHF if DOX was administered and continued without LVEF monitoring. Thus, in the sample of patients considered in the effectiveness study, CHF would have developed in 20 patients (50% of 41 "at-risk" cases). Consequently, serial ERNA monitoring
would prevent 15 potential CHF cases and would miss 2 cases.

Measure of benefits used in the economic analysis
No summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was carried out.

Direct costs
Discounting was not relevant since the costs were incurred during one year. The unit costs were not presented separately from the quantities of resources used. A detailed breakdown of the cost items was not reported. The economic evaluation considered ERNA studies and all the services associated with caring for CHF patients in the USA. The cost/resource boundary adopted in the study was not stated. The unit cost of an ERNA study was derived from Medicare reimbursement, but details on the services considered in the management of CHF were not reported. The number of ERNA studies required was derived from the sample of patients included in the effectiveness study. The source of the annual cost of caring for CHF patients was derived from studies published between 1994 and 1998. The price year was not reported.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not carried out.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The authors stated that, by using ERNA studies, the total prevented cost of caring for an additional 15 CHF cases would be $150,000 to $250,000 per year in comparison with a strategy of not monitoring patients.

The total cost for ERNA procedures was approximately $212,000. This is almost equal to (or less than) one year’s cost of caring for the number of potential CHF patients presumed to be prevented by the present monitoring system.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant because a cost-consequences analysis was carried out.

Authors’ conclusions
Left ventricular ejection fraction (LVEF) monitoring using equilibrium radionuclide angiography (ERNA) led to a reduced frequency of doxorubicin (DOX)-induced congestive heart failure (CHF), without increasing the costs of care, in patients with cancer who were undergoing chemotherapy.
CRD COMMENTARY - Selection of comparators
The comparator selected in the analysis reflected the management of patients without LVEF monitoring using ERNA. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence on LVEF monitoring was derived from a retrospective review of patients' charts, which represents a weak source of evidence. Clinical data on the comparator were based on authors' assumptions. The use of a prospective, comparative study would have been more appropriate. Further, the evidence came from a single centre, which does not ensure it is representative of the study sample. A small sample of patients was included in the sub-group analysis.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The authors did not state which perspective was adopted in the study. The annual cost of managing a CHF case was estimated from published studies, and a breakdown of the cost items was not given. This reduces the possibility of replicating the study. Similarly, the price year was not reported, thus hampering reflation exercises in other settings. Only the unit cost of an ERNA study was given. This was derived from the payer's reimbursement rates.

Other issues
The authors did not compare their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. Sensitivity analyses were not performed, which reduces the external validity of the study.

Implications of the study
The study results supported the use of LVEF monitoring with ERNA to prevent cardiac morbidity and mortality from DOX chemotherapy.

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None stated.

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Other publications of related interest
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