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Cost-effectiveness of strain-targeted cardioprotection for prevention of chemotherapy-induced cardiotoxicity

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ABSTRACT

Background: Cancer chemotherapy increases the risk of heart failure. This cost-effectiveness model compared strain-guided cardioprotection with other protective strategies using a health care payer perspective and five-year time horizon.

Methods: Three cardioprotection strategies were assessed: 1) usual care (EF-guided cardioprotection, EFGCP) with cardioprotection initiated on diagnosis of LVEF-defined cardiotoxicity (EF-CTX), 2) universal cardioprotection (UCP) for all such patients, and 3) strain-guided cardioprotection (SGCP — treatment of patients with subclinical cardiotoxicity [S-CTX]). A Markov model, informed by the published literature on transitional probabilities, costs and quality-adjusted life years (QALYs) was developed to assess the incremental cost-effectiveness ratio (ICER). Costs, effects and ICER of each specified cardioprotective strategy were assessed over a 5-year range, with sensitivity analyses for significant variables.

Results: In the reference case of a 49 year old woman with stage IIb breast cancer treated with sequential anthracyclines and trastuzumab, strain-guided cardioprotection (3.79 QALYS and $4159 cost over 5 years) dominated both UCP (3.64 QALYs and $5967 cost over 5 years) and EFGCP (3.53 QALYs and $7033 cost over five years). Model results were dependent on the probabilities of patients developing subclinical LV dysfunction, with UCP dominating alternative strategies at probabilities ≥51%. Variations in the cost of cardioprotective medications and probabilities of cardioprotection side-effects had no effect on model conclusions.

Conclusions: In patients at risk of chemotherapy-related cardiotoxicity, strain-guided cardioprotection provides more QALYs at lower cost than standard care or uniform cardioprotection.

Advances in cancer management over recent decades have led to an increasing proportion of cancer survivors. Chemotherapy and radiotherapy (especially in combination) are associated with cardiac dysfunction in up to 26% of treated patients by six months [1] and symptomatic heart failure in up to 20% at 5 years [2] depending on the dose and type of chemotherapy. Heart failure in this setting has a two-year mortality of up to 50% [3]. The current standard of care involves regular monitoring of left ventricular ejection fraction (LVEF), with initiation of heart failure medications once LVEF drops to the point when cardiotoxicity (conventionally defined as an asymptomatic drop of LVEF by ≥10% to final value of <55% or a symptomatic drop of LVEF by ≥5% to final value of <55%) is diagnosed [4]. This LVEF-guided definition of cardiotoxicity (EF-CTX) is a late stage of progressive myocardial functional impairment initiated at the time of cardiac insult [5]. An alternative strategy, based on a small randomised controlled trial of pre-emptive treatment of all patients with maximum tolerated doses of enalapril and carvedilol at the time of chemotherapy, has been demonstrated to reduce the incidence of cardiotoxicity and symptomatic heart failure compared with a control group [6]. The disadvantage of this approach is that most treated patients do not develop EF-CTX or symptomatic heart failure and would have unnecessarily been exposed to the potential side-effects and cost of medications.

A third strategy would be to use a highly sensitive test to identify high-risk subgroups within the chemotherapy-treated population, and initiate cardioprotection only in these patients. This could provide the health benefits of cardioprotection while minimizing unnecessary medication costs and side-effects. Global longitudinal strain (GLS) derived from speckle-tracking echocardiography is a novel non-invasive imaging technique that quantitatively measures regional myocardial deformation, a sensitive marker of myocardial function. Strain can identify

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early pathological changes in myocardial systolic function before any appreciable decline in LVEF becomes apparent, has been demonstrated to be a stronger predictor of outcome than EF, and can accurately predict development of cardiotoxicity [5]. This stage of subclinical cardiotoxicity (S-CTX) identifies a population at high risk of EF-CTX and symptomatic heart failure, and may represent an attractive opportunity for targeted cardioprotection (CP). No randomized trial has compared these options, so we developed a Markov model to incorporate probabilities and risks of three cardioprotection strategies to determine the costs and quality-adjusted life-years (QALYs) obtained by each strategy in patients treated with potentially cardiotoxic chemotherapy.

1. Methods

1.1. Model design

This decision-analytic model evaluated the morbidity, mortality, and costs inherent in three clinically-relevant strategies; 1) the current standard strategy of initiating cardioprotection medications after diagnosis of EF-CTX (diagnosed as an asymptomatic decline in LVEF by >10% to value of <55%) or symptomatic heart failure, 2) a strategy of uniform cardioprotection (UCP) for all patients at the time of chemotherapy, and a 3) a strategy of using S-CTX (defined as a decline in global longitudinal strain (GLS) of ≥11% from baseline by 3 months post chemotherapy-initiation) to commence cardioprotection treatment. Cardioprotection was defined as concurrent enalapril and carvedilol up-titrated to their maximum dose, as used in the active treatment arm of a large recent randomised controlled trial [6], and used throughout the 5-years of modelling. Correction factors for time lapsing were used if cardioprotection was commenced after echocardiographic or clinical findings. This Markov model used Monte Carlo simulations (TreeAge Software Inc. Williamtown, MA), to assess the clinical and economic consequences of alternative strategies of using cardioprotective strategies in a hypothetical cohort of 10,000 patients in a microsimulation model without tracker variables [11]. Beta distributions were assigned to probabilities and utilities, and gamma distributions for costs based on standard errors derived from the associated literature. Means and 95% credible intervals (95% CI) were computed on the basis of 10,000 μ-simulations. Cost-effectiveness acceptability curves (CEACs, a method to quantify and graphically represent uncertainty in economic evaluation studies of health-care technologies) were used to report the probability that the ICER for an intervention was below the predefined willingness to pay threshold. This study was performed in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines, as detailed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

We estimated costs and benefits of the interventions (deaths averted and quality-adjusted life-years [QALYs] gained) over a 5-year period of the cohort, because transition probabilities beyond this period are not currently well-described. We assumed that all interventions took place at the start of the time horizon, and discounted all future costs and benefits by 3% per annum. Cycle length is the time-frame of transition from one state to the next, during which period all information is held constant. For the purposes of this analysis, cycle length was assumed to be 1 year.

1.2. Decision tree

The Markov model (Fig. 1) accounted for the dynamics of cardiac screening and utilization of cardioprotective medications in a cohort of 10,000 patients scheduled to receive chemotherapy for cancer. The base case (a 49 year old woman with stage II breast cancer receiving sequential anthracycline and trastuzumab therapy) was applied to all cohort patients. At commencement of the time horizon, this hypothetical individual was assigned to one of the three screening strategies. These patients progressed through the Markov model on the basis of transition probabilities (Table 1), informed by utilities (Table 2) and costs (Table 3).

The model was intended to capture the high-level costs and effectiveness of screening and treating a large cohort. In sensitivity analysis, we considered a range of values reported in scientific literature for transition probabilities, costs and utilities. Where data were available, low and high values were chosen to reflect ranges in the literature. The model structure was based in part on other models in the literature, and was reviewed by clinicians involved in the care of cancer patients and chemotherapy-related cardiotoxicity.

1.3. Health states and transitions

Data on transitions between health states were obtained from the literature and expert sources (Table 1);

The *asymptomatic post-chemotherapy* state described patients without any cardiac symptoms or apparent structural changes on cardiac imaging.

Asymptomatic cardiotoxicity (referred to in this study as EF-CTX) was identified in patients with a ≥ 10% asymptomatic drop of LVEF.

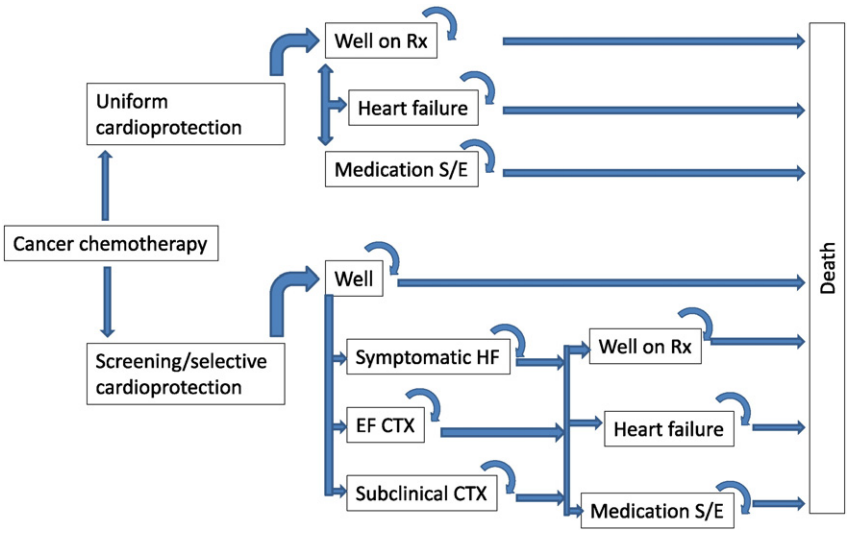

Fig. 1. Bubble diagram demonstrating the transition states incorporated into Markov model.