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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, 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 year). 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.

Keywords: chemotherapy, cardiotoxicity, decision-making, cost effectiveness.

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 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,[7] 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 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.

Methods

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 micro-simulation model without tracker variables. 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 micro-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.

Decision tree. The Markov model (Figure 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.

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.

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.

Subclinical LV dysfunction (referred to in this study as S-CTX) was diagnosed in patients without EF changes but with a ≥11% reduction of GLS. We restricted this analysis to GLS rather than circumferential or radial strain, as the former is used in the guidelines and there is no evidence that the latter are more effective for this purpose.[5]

Other health states were *heart failure* and *death.* The background mortality rate was calculated from USA life tables specific to the base case of breast cancer or scenario analyses of other cancers (www.cdc.gov/nchs/products).

Transition probabilities were separated into the categories of initial year of treatment, and for subsequent years. Further details regarding mortality in each health state is provided in the next section.

Costs. We conducted our economic analysis from the perspective of the healthcare payer and therefore used the amount reimbursed to the provider as the cost of care. Information regarding costs was obtained primarily from the literature, including diagnostic related groups (DRGs), Medicare payments for current procedural terminology (CPT) codes and discounted drug prices (Table 3). LVEF-guided echocardiographic screening costs were calculated by taking the CPT reimbursement cost[8] and assuming a regimen of five echocardiographic studies (baseline and 3-monthly in the first year only). Strain-guided echocardiographic screening costs were calculated using the same CPT cost, but assuming the performance of monthly echocardiographic studies in the first year – which is the maximum that might be anticipated with trastuzumab therapy after anthracyclines. Medication costs were obtained from the Walmart Retail Prescription program drug list[9]. Costs of routine biochemical or haematological screening for medication side-effects were not included as it was considered likely that patients receiving chemotherapy would receive regular investigations regardless of whether they received cardioprotective medications. Costs were expressed to 2015 US$ and a willingness to pay threshold of $53,000 per QALY was applied, as this represents the 2015 average annual gross domestic product (GDP) of the US and a national GDP value per capita has been suggested by the World Health Organization to represent how much a nation can reasonably be spend to save each QALY[9]. The costs published in the literature more than two years earlier were corrected for intervening currency fluctuations using a commercial past currency converter (www.fxtop.com/en/currency-converter-past.php).

Health outcomes. Information regarding health outcomes was obtained from searches linking health states with the words "utility" and "quality of life" (QOL). Table 1 lists the findings for utilities (values obtained from preferences associated with health-related quality of life where full health = 1.0 and dead = 0.0).

Sensitivity analysis. Critical sources of variation in the input data were gathered by one-way sensitivity analyses, varying each input factor by its standard error. A threshold analysis was performed on the most influential factors to identify the point where the additional cost per QALY was <$53,000. The Net Monetary Benefit (NMB) was defined as the difference between the gain in QALYs and the ratio between the willingness to pay threshold and the difference in cost. Because of concerns regarding model sensitivity to synergistic influences of cardioprotective side-effects on costs and health-state utilities (as these represent the only trade-offs for uniform use), these transition probabilities were subject to two-way sensitivity analyses.

Scenario analysis. To determine the applicability of cost-effectiveness of cardioprotective strategies for high-risk cancer patient subgroups other than breast cancer, two additional scenario analyses were run using the same Markov model. The first scenario utilized a reference case of a 50 year-old man with stage III non-Hodgkin's lymphoma and a low-to-intermediate International Prognostic Index score. The second scenario utilized a reference case of a 48 year old man with acute myeloid leukaemia. Both cases involved treatment with anthracyclines. Transition probabilities and mortality rates were utilized from published literature and transition probabilities of significant GLS drop were utilized from subgroups of trials (see Online Appendix 1).

Internal model validation: Markov model validation was performed as advised by ISPOR guidelines[10]. In the base case analysis, distributions were sampled 100 times, and after each sample, 1000 trials were run using values drawn from each sample in order to calculate the mean costs and effectiveness. For internal validity, we compared the life-expectancy generated by our Markov model with life-expectancy of non-metastatic breast cancer patients with clinical characteristics as our base case reported in the US Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute. Goodness of fit was predicted by plotting model predictions versus SEER database observed data and fitting a linear curve through points with an intercept of zero. The squared linear correlation coefficient (R^2), obtained using linear regression, was used as an index of association. External validation was not performed, due to insufficient studies which were not included in the Markov model construction.

Results

Health outcomes and costs. In the reference case (49 year old woman taking anthracycline and trastuzumab for breast cancer, annual cost of cardioprotective medication of $81 with 56% probability of medication side-effects, leading to 38% overall abandoning cardioprotection), the outcomes of SGCP (3.73±0.87 QALYs, $4161±$3997 over 5 years) were superior to those of UCP (3.64±0.75 QALYs, $5,753±$5840) and EFGCP (3.53±0.86 QALYs, $6820±$6450). Both UCP and EFGCP were dominated by SGCP strategy.

Sensitivity analyses. One-way sensitivity analyses were performed over a clinically plausible range for all variables. The impact of these variations on health outcomes is depicted in a tornado diagram (Figure 2). This sensitivity analysis revealed that the variables that had the largest impact on model outcomes were probability and utility of S-CTX, medication side-effects and cost of managing those side-effects.

One-way sensitivity analysis of probability of a decrease in GLS revealed a strong impact on model's conclusions (Figure 3). At S-CTX transition probabilities of ≤34%, SGCP dominated alternative strategies. Above these transition probabilities, UCP delivered higher net monetary benefits. EFGCP did not provide superior benefits at any level of transition probability.

The impact of parameter uncertainty in the frequency of side-effects and the cost of side-effects was explored further in an additional sensitivity analysis across the plausible range of the frequency and cost of side-effects (Figure 4). This showed that SGCP dominated both UCP and

EFGCP throughout the plausible ranges of medication side-effects transition probabilities and costs.

Monte Carlo simulation. The impact of parameter uncertainty in the frequency of transition probabilities, utilities and costs were examined using a Monte Carlo analysis with 10,000 simulations. This demonstrated that SGCP was the optimal strategy, with a mean survival of 4.66 years with SGCP, 4.56 years with UCP and 4.48 years with LVGCP.

A cost-effectiveness acceptability curve (Figure 5) demonstrated that strain-guided strategy was consistently the most cost-effective strategy across a broad plausible range of willingness-to-pay thresholds (from \$0 to \$100,000 per annum). An incremental cost-effectiveness scatterplot of results of 1000 pairs of differences in costs and QALYs shows that both SGCP (Figure 6a) and UCP (Figure 6b) are more cost-effective than the current standard of care (EFGCP). The comparison between SGCP and UCP (Figure 6c) does not show clear benefit for either approach, with SGCP being more cost-effective in 56% of instances.

Scenario analysis: In a scenario analysis examining the cost-effectiveness of imaging-guided CP strategies in haematological malignancies, the index case consisted of a 50 year old man with stage III non-Hodgkin's lymphoma. Transition probabilities were altered to reflect the higher incidences of cardiovascular complications (Online Appendix 1) due to more aggressive chemotherapeutic regimens. The most significant change consisted of increase of cardiotoxicity in absence of CP from 20% to 36%. An incremental increase in costs and QALYs gained with SGCP (ICER \$18,264 per QALY gained) with overall higher costs and lower QALY per strategy was seen than with breast cancer reference case (over a five-year period, SGCP 3.49±0.72 QALYs, \$23,012±31,611; UCP 3.24±1.45 QALYs, \$18,400±27,538; EFGCP 3.15±0.89 QALYs, \$27,537±25,528). These findings are broadly similar to those of the base case of the main study with the ICER for SGCP falling below WTP threshold. The second index case, a 45 year-old man with acute myeloid leukaemia, demonstrated extended dominance by UCP over both alternative strategies (over a five-year period, UCP 2.97±1.07 QALYs, \$26,458±22,941; SGCP 2.87±1.29, \$48,997±30,992; EFGCP 2.86±1.10 QALYs,

\$31,114±31,092). There was no clinically significant difference in QALYs gained between SGCP and EFGCP in this scenario.

Model validation: The results generated by the model closely match the input data from which the input probabilities were derived: the linear regression slope was close to 1 (1.04, $p<0.001$), and the adjusted R^2 was 0.9993 ($p<0.001$), demonstrating that the model faithfully reproduced the published data. For the first scenario analysis, the linear regression slope was 2.71, and adjusted R^2 was 0.9559 ($p<0.001$). For the second scenario analysis, linear regression slope was 1.41, and adjusted R^2 was 0.9376. This suggests good model approximation to observed life expectancy in studies utilised for the model.

Discussion

In this analysis of the cost-effectiveness of three strategies for targeting cardioprotective medications for the prevention of chemotherapy-related cardiomyopathy, global longitudinal strain provided additional QALYs at lesser cost compared with UCP and LVGCP. SGCP also produced the highest value of 5-year survival, and was the optimal strategy in the majority of Monte Carlo simulations. The increased 5-year survival reflects the high mortality burden of heart failure, even small reductions in incidence of heart failure complicating chemotherapy can affect population survival rates. Sensitivity analyses demonstrated that cost-effectiveness was highly dependent on probability of reduced GLS. Scenario analyses revealed similar findings for an index case of non-Hodgkin's lymphoma, but UCP was found to dominate both alternative strategies in the case of acute myeloid leukaemia. This is likely due to the higher incidence of reported cardiotoxicity and heart failure due to more aggressive chemotherapeutic regimens, which would lead to greater clinical benefit from a UCP approach. The conclusions of the model were robust when tested with sensitivity analyses, with a change in conclusions only if the incidence and cost of cardioprotective side-effects increased.

Cardiotoxicity from cancer chemotherapy Both European and US cardiovascular society guidelines recognize the need to monitor and manage this patient subgroup[13] although they do not make specific recommendations regarding strategies for targeting therapy. The large population at risk of chemotherapy-related cardiomyopathy, the time difference between chemotherapy and onset of cardiomyopathy symptoms and the high morbidity and mortality associated with the condition suggest that the financial and health burden that it places on society is likely underestimated, and a cost-effective method of decreasing its incidence could translate into tangible and wide-reaching benefits for healthcare systems as a whole. Specialized cardio-oncology clinics have been created in many countries in recognition of the special cardiovascular challenges of cancer survivors, and this analysis adds to the growing published literature, showing that promoting optimal cardio-oncology practice can provide both health and cost benefits.

Strain-guided management. The adoption of strain guided therapy places little financial burden on the healthcare system, as it requires only an update in echocardiography software and a modest time investment in training for sonographers and cardiologists. This training would likely have additional benefits in a cardiology practice, as 2D strain echocardiography has shown clinical benefit in diagnosis and prognosis of many cardiac diseases.

As the majority of costs in the models relate to managing chemotherapy-related cardiovascular complications arising either from HF, or alternatively managing predictable side-effects of medications, a method of minimizing HF by treating the smallest possible at risk group could be expected to be optimal. Strain identifies a population with subclinical dysfunction who are at-risk of overt CTX, thereby targeting patients most likely to benefit from cardioprotection. The current strategy of EFGCP does not represent an effective use of healthcare resources, as therapy is targeted towards an advanced disease subgroup in which up to 58% of patients may not respond[14]. In contrast, sensitivity analysis showed that the cost-effectiveness of SGCP remained below the conservative willingness-to-pay threshold of $53,000 even if the transition probability of cardiotoxicity was equal or higher than 45%.

Scenario analysis: Scenario analyses were also conducted to investigate the cost-effectiveness of these cardioprotective strategies in haematological malignancies. These malignancies differ from breast cancer in having higher annual mortality rates, and also higher incidences of cardiotoxicity and cardiac failure due to more aggressive chemotherapeutic regimens[15]. For non-Hodgkin's lymphoma (NHL), the results were broadly similar to those of breast cancer, with SGCP offering incremental clinical benefit over UCP at higher costs. The ICER was higher for NHL ($15,251/QALY vs. $3,906/QALY), which was driven by a higher background mortality rate. For the scenario analysis of a man with AML, the high five-year mortality mitigated any clinical benefit from a cardiac imaging strategy, and UCP dominated both alternative strategies. These results suggest that significant differences may exist in cost-effectiveness of strategies depending on malignancy involved. However only strain echocardiography findings in haematological malignancies are limited to small subgroups of trials that predominantly recruited breast cancer patients, so at present the findings of these scenario analyses should be considered hypothesis-generating.

Assumptions. Strengths of this analysis include accounting for a spectrum of cardiotoxicity after chemotherapy, explicitly accounting for changes in costs and quality-of-life due to cardioprotective treatment and accounting for changes in incidence of conditions in first and then subsequent years. Nonetheless, the value ranges were drawn from retrospective data from different studies involving different populations and time-periods. Generally, when a range of transition probabilities and outcomes was considered, we used the most conservative assumptions. For example, we assumed cost for an annual cardiac screening regimen utilizing 2D-strain echocardiography to be five times higher than for a regimen using LVEF echocardiography, although the two techniques are approximately similar in terms of infrastructure and training. It is also entirely possible that 2D-strain echocardiography could reduce the need for further cardiac screening after three months due to its inherently higher sensitivity, which would significantly reduce costs and improve net monetary benefits associated with SGCP. However large clinical-outcome driven trials assessing shorter cardiac imaging protocols are yet to be conducted. Because some of these strategies are novel (e.g. strain echocardiography), clinical trials have been mostly small-scale and single centre. However these trials have consistently reported similar findings, and sensitivity analyses of these variables did not substantially change the study's conclusions.

Publications detailing costs of adverse drug reactions are scarce in scientific literature, and most studies examined emergency or hospitalized patients. We recognise that this could potentially be a source of discrepancy between our model and current clinical practice. However, side-effects of ACE inhibitors and β-blockers encompass a spectrum that include life-threatening side-effects, and even milder side-effects may necessitate emergency room visits and expensive further investigations.

Rare outcomes (e.g. death) were frequently not reported in these single-centre trials, and we needed to extrapolate from larger observational trials in which patient population characteristics differed in several regards. Additionally, costs of medical care and conditions differ in different countries and in different medical contexts (outpatient care, hospital inpatient care), which could affect modelling results.

A health-payer perspective was taken, in order to make this study highly applicable for health-care managers and decision-makers. We recognise that a societal perspective may confer some advantages, such as detecting cost-shifting between sectors, but we think this is unlikely in this particular clinical setting. Changes in utility values for health states in sensitivity analyses had little effect on cost-effectiveness ratios and, in all cases the current strategy of LVEF-guided therapy was dominated with strain-guided therapy providing additional QALYs at modest additional cost. We also did not alter the baseline patient utilities to include reduced utilities of non-metastatic breast cancer diagnosis. The reason is that because the aim of the study was to assess three different strategies, and applying breast cancer utilities would have added an unnecessary extraneous variable which would not alter the conclusion, as it would apply equally to all three strategies. Additionally utility values quoted in the literature for adjuvant chemotherapy for breast cancer are in the range of 0.94 – 0.99[41], so would not be expected to significantly change final derived utilities.

Limitations. The specific clinical characteristics of the chosen index case and scenario analyses may limit the applicability of this study to a selection of cardio-oncology cases. This is unavoidable, as the wide spectrum of cancers treated with anthracyclines, the variability of chemotherapy regimens, the different cardiac screening modalities and regimens available, and different cardioprotection strategies available (including dexrazoxane) and the decision whether to continue chemotherapy would introduce so many variables that the model's conclusions would lose applicability to specific patient subgroups. Nevertheless, we feel that our model encompasses the most common clinical scenarios.

The use of troponin measurements for predicting cardiotoxicity represents an alternative strategy. However, studies of the utility of troponin for targeting cardioprotective medications tested a population treated with relatively high doses of anthracyclines[16], with mean cumulative anthracycline doses of approximately 350 mg/m^2. A subsequent study that investigated a strategy of concurrent strain echocardiography and ultrasensitive troponin I measurements for predicting cardiotoxicity in a population treated with low-to-moderate anthracycline doses found that in multivariate analysis, strain was an independent predictor of later cardiotoxicity, but troponin was not[17]. For these reasons, we did not include troponin measurements into our model.

Clinical relevance. The strategy of a screening process with strain imaging may be applicable to other situations where there is a risk of developing HF. Heart failure management costs the US economy $53 billion/year[18], and treatments that reduce its incidence have the potential to be substantially cost-saving. Use of 2D strain echocardiography would represent an investment in potentially improving outcomes and reducing future healthcare costs of HF.

Conclusions. A strain-guided strategy for targeting cardioprotective medications for patients at risk of chemotherapy-related cardiotoxicity provides more QALYs at lower cost than standard care, and provides more QALYs at a reasonable additional cost compared with uniform CP strategy.

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Figure legends

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

Figure 2: Tornado diagram demonstrating influence of cost, utilities and transition probabilities on expected value, assuming a willingness-to-pay value of US$53,000. EF-CTX –cardiotoxicity with reduced ejection-fraction, HF – symptomatic heart failure, S-CTX – subclinical cardiotoxicity, UCP – uniform cardioprotection

Figure 3: One-way sensitivity analysis evaluating net monetary benefits (NMB) across a range of transition probabilities of patients having detectable subclinical cardiotoxicity when utilizing a strain-guided strategy (SGCP). A willingness-to-pay threshold of $53,000 was assumed. At probability values higher than 28.8%, uniform cardioprotection (UCP) yielded higher NMB than SGCP.

Figure 4: Two-way sensitivity analysis comparing net monetary benefits (NMB) from the annual cost of medication side-effects (US$) and the transition probability of medication side-effects. At annual side-effect costs <$5242, uniform therapy is more likely to provide higher NMB values than alternative strategies, and this threshold decreases as side effect probability increases.

Figure 5: Cost-effectiveness acceptability curve representing the probability that each treatment strategy is cost-effective for a given maximum willingness-to-pay threshold per QALY gained. The graph is based on 10,000 Monte Carlo simulations, drawing parameters for each input from probability distributions

Figure 6: Incremental cost-effectiveness boot strap scatterplot. The y-axis represents the difference in mean costs (2015 US$) between strain-guided therapy and uniform therapy strategies, and the y-axis represents the difference in mean QALYs. Quadrant 1 represents iterations for which new strategy is more expensive and less efficacious (i.e. inferior) than it's comparator. Quadrant 2 represents iterations for which the new strategy provides additional QALYs at additional cost (cases below the willingness-to-pay (WTP) line represent iterations where this additional cost is deemed desirable. Quadrant 3 represents iterations where the new strategy is less expensive and less efficacious than the comparator. Quadrant 4 represents iterations where new strategy was less expensive and more efficacious (i.e. superior). The ellipse represents the region containing 95% of iterations.

- **A)** Strain-guided cardioprotection strategy **(**SGCP) vs ejection-fraction guided cardioprotection strategy (EFGCP). 94.9% of iterations were either superior (15.1% of iterations), or provided additional QALYs at additional cost that was less than WTP (79.8%).
- **B)** Uniform cardioprotection (UCP) ejection-fraction guided cardioprotection (EFGCP). In 88.4% of iterations, UCP provided additional QALYs at additional cost but remained below the WTP threshold.
- **C)** SGCP vs UCP. In 55.9% of iterations, the SGCP strategy yielded either higher QALYs at lower cost (39%) or at additional cost that was below WTP (21.2%).

Online Appendix 1

Table 1. Values for model variables.

Variable	Base value	Range		Source
		Minimum	Maximum	
Annual Transition Probabilities				
Initial Year				
Probability of global longitudinal strain (GLS) drop after chemotherapy	0.23	0.23	0.51	[7, 10]
Patients with GLS drop (S-CTX);				
-Cardiotoxicity (EF-CTX)	0.25	0.2	0.5	[17, 19, 20]
-Cardiac Failure	0.02	0	0.14	
-Cardaic Death	0.01	0	0.02	
Patients without GSL drop;				
-Cardiotoxicity (EF-CTX)	0.01	0.005	0.0015	[17, 19, 20]
-Cardiac Failure	0.005	0.001	0.0015	
-Cardic Death	0.005	0.001	0.0015	
Patients on uniform therapy;				
-Cardiotoxicity	0.1	0	0.35	[16, 21, 22]
-Cardiac Failure	0.03	0	0.05	

-Death	0.01	0	0.05	
EF-guided strategy; -Cardiotoxicity -Cardiac Failure -Death	 0.2 0.05 0.03	 0.05 0.01 0	 0.3 0.2 0.1	[6, 16, 23]
Cardioprotective Medication Side-Effects	0.33	0.25	0.64	
Cardioprotective Medication discontinuation	0.1	0.05	0.13	
Years 2-5				
Patients without GLS drop				
-Cardiotoxicity	0.005	0.001	0.009	*
-Cardiac Failure	0.001	0.0005	0.0015	*
-Cardiac Death	0.001	0.0005	0.0015	*
Patients with GLS Drop (S-CTX)				
-Cardiotoxicity	0.008	0.005	0.015	*
-Cardiac Failure	0.002	0.001	0.003	*
-Cardiac Death	0.001	0.005	0.0015	*
Clinically Well Patients				
-Cardiotoxicity	0.03	0.01	0.05	[6,16,23]
-Cardiac Failure	0.01	0.005	0.015	[6,16,23]
-Cardiac Death	0.005	0.001	0.009	[6,16,23]
Cardioprotective Medication Side-Effects	0.2	0.1	0.3	*
Cardioprotective Medication Discontinuation	0.05	0.02	0.08	*

Cardiotoxicity Patients (EF-CTX)				
Congestive Cardiac failure	0.026	0.0	0.052	*
Death	0.04	0.0	0.08	*
Costs (annual, 2015 US$)				
Strain-Guided Echocardiographic Screening	5127	2000	8000	[8]
LVEF-Guided Echocardiographic Screening	2564	1000	3000	[8]
Cardiotoxicity	1800	1000	5000	[24, 25, 26]
Cardiac Failure	7000	5000	20000	[27, 28]
Death	40000	10000	92000	[29, 30, 31]
Cardioprotective Medications	81	81	800	[9]
Cardioprotective medication side-effects	750	50	5000	[32, 33]
Utilities				
Cardiotoxicity	0.94	0.68	0.99	[34, 35, 36]
Cardiac Failure	0.6	0.52	0.74	[35, 37, 38]
Death	0	0	0	*
Medication side-effects (medication continued)	0.96	0.92	1.0	[39]
Medication side-effects (medications ceased)	0.99	0.95	1.0	[40]

- * represents expert opinion in the context of insufficient information in published literature due to low incidence (typically <1%) in small trials
- EF-CTX refers to cardiotoxicity, as diagnosed by Seidman et al[4], as either an asymptomatic decline in left ventricular ejection fraction of ≥10% or a symptomatic decline of ≥5%.

- S-CTX refers to patients who develop as a decline in global longitudinal strain (GLS) of ≥11% from baseline by 3 months post chemotherapy-initiation

Online Appendix 2

Scenario analysis 1: Index case of a 50 year-old man with stage III Non-Hodgkin's Lymphoma and low-to-intermediate IPI risk.

Variable	Base value	Range		Source
		Minimum	Maximum	
Annual transition probabilities				
Patients with S-CTX: -Cardiotoxicity - Cardiac Failure	 0.40 0.05	 0.20 0.01	 0.60 0.10	[1] [2]
Patients on uniform therapy -Cardiotoxicity - Cardiac Failure	 0.15 0.05	 0.10 0.01	 0.20 0.10	[1]
Patients on LV-guided cardioprotection: -Cardiotoxicity - Cardiac Failure	 0.36 0.05	 0.20 0.01	 0.52 0.10	[3]
Mortality rates: First year Second year Third year Fourth year Fifth year Cumulative five-year mortality	 4.6% 6.2% 0.7% 4.1% 5.2% 20.8%			[4]

Scenario analysis 2: Index case of a 45 year old man with acute myeloid leukemia.

Variable	Base value	Range		Source
		Minimum	Maximum	
Annual transition probabilities				
Patients with S-CTX: -EF-CTX -Cardiac Failure	 0.40 0.05	 0.20 0.01	 0.60 0.10	[1] [2]
Patients on uniform therapy: -EF-CTX -Cardiac Failure	 0.15 0.05	 0.10 0.01	 0.20 0.10	[1] [2]
Patients on LV-guided strategy: -EF-CTX -Cardiac Failure	 0.18 0.05	 0.20 0.01	 0.52 0.10	[3]
Mortality rates: First year Second year Third year Fourth year Fifth year Cumulative 5 year mortality	 33% 5% 5% 5% 5% 52%			[4]

Online Appendix references

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