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RESEARCH PAPER

Model-Based Evaluation and Optimization of Cardiac Monitoring Protocols for Adjuvant Treatment of Breast Cancer with Trastuzumab

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ABSTRACT

Purpose Trastuzumab treatment is associated with occurrence of cardiac toxicity, for which monitoring of the left ventricular ejection fraction (LVEF) is indicated. The performance of the currently used monitoring protocol as defined in the summary of product characteristics (SPC) is however unknown. The objective of this analysis was to develop a model-based framework for evaluation and optimization of cardiac monitoring strategies.

Methods The model-based framework comprised a previously developed exposure-response model for trastuzumab induced changes in LVEF, and a protocol-execution model that allowed incorporation of treatment interventions as described by a monitoring protocol. Metrics for evaluation of toxicity, dose intensity and monitoring burden were defined to allow evaluation and optimization of cardiac monitoring protocols.

Results The success of a protocol-defined dose reduction was improved from 40% for the SPC-based protocol, to 79% for a scoring-based protocol, thereby decreasing the observed severity of cardiotoxicity. Including adaptation based on risk-profile allowed reduction of the mean number of LVEF measurements by 19%.

Conclusions This model-based evaluation approach enabled evaluation and optimization of cardiac monitoring protocols that would be difficult to evaluate in a clinical setting. This approach can potentially be applied for other drugs that use repeated evaluation of continuous biomarkers for toxicity.

KEY WORDS cardiac monitoring · cardiotoxicity · left ventricular ejection fraction · modelling · trastuzumab

ABBREVIATIONS

AUC_{45}	area below a LVEF threshold of 45% and above the LVEF time curve
FT-AUC_{45}	full-treatment AUC_{45}
LVEF	left ventricular ejection fraction
O-AUC_{45}	observed AUC_{45}
PD	pharmacodynamics
PK	pharmacokinetics
SPC	summary of product characteristics

INTRODUCTION

Trastuzumab and Cardiac Toxicity

Trastuzumab is a monoclonal antibody that selectively binds to the extracellular domain of the HER2 receptor, and improves outcome in early and advanced HER2+ breast cancer (1–3). Adjuvant trastuzumab treatment of primary HER2+ breast cancer comprises weekly or three-weekly dosing schedules for the duration of one year, partly

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in combination with chemotherapy. The most commonly used dosing schedules for adjuvant trastuzumab treatment include: i) doxorubicin plus cyclophosphamide, followed by trastuzumab plus docetaxel, ii) trastuzumab combined with docetaxel and carboplatin, and iii) as trastuzumab monotherapy.

Trastuzumab treatment is associated with cardiac dysfunction, which most frequently manifests by the occurrence of asymptomatic declines in LVEF, and less frequently by an increased incidence of development of congestive heart failure (2–4%)(4–6). Trastuzumab induced cardiotoxicity is likely to be related to involvement of the HER2-receptor in the (patho-) physiology of heart muscle contractility; however, the exact mechanism remains to be elucidated (7,8). Unlike cardiac dysfunction induced by anthracyclines, trastuzumab induced cardiac dysfunction is at least partly reversible (9–12). Moreover, an increased incidence of cardiotoxicity has been reported for patients treated with anthracyclines both prior to (10,12,13), as well as concurrently with trastuzumab (2). Moreover, the risk for cardiotoxicity has been reported to increase with age (14).

Cardiac Monitoring Strategies

Given the expected length of survival of patients receiving adjuvant trastuzumab treatment, it is important to carefully monitor cardiac function in order to ensure that no substantial cardiac damage is acquired. Therefore, a well-performing monitoring protocol should identify patients with potentially harmful cardiac toxicity, while allowing other patients to receive the full treatment cycle.

The advised strategy for monitoring of cardiac function is described in the summary of product characteristics (SPC) of trastuzumab (15). This monitoring protocol is based on 3-monthly evaluation of the LVEF, with an interruption or termination of treatment if a cardiac event occurs. For this protocol, a cardiac event was defined as a drop >10% from the baseline LVEF, accompanied by a LVEF <50%.

There are however, a number of potential problems are associated with this SPC-based strategy. For instance, the diagnostic performance with respect to the correct identification of patients at risk for cardiotoxicity is unclear. The schedule does not take into account the uncertainty associated with a single point measurement. Additionally, the current monitoring protocol is not adaptive. This is relevant because the majority of the patients do not develop any cardiotoxicity during treatment (e.g. congestive heart failure in 2–4% of patients), but are nonetheless exposed to a number of burdensome and costly LVEF evaluations. Finally, the SPC protocol allows treatment interventions which could be considered as sub-optimal. For example, according to the SPC protocol, a patient whose LVEF drops from 51 to 42% during 3 months does not need to stop, but a patient whose LVEF drops from 59 to 48% is required to stop trastuzumab treatment.

Thus, it would be useful to evaluate the performance of the currently used SPC-based monitoring protocol, with respect to some of these issues, and also to determine if the monitoring strategy can be further optimized. However, informative evaluation of repeated measurements of LVEF monitoring is not considered feasible when conducted in an actual clinical trial setting, both due practical and technical limitations.

Model-Based Evaluation

Recently, we have developed a population pharmacokinetic-pharmacodynamic (PK-PD) model that describes the relationship between trastuzumab exposure and the associated decline in LVEF (12). In the current analysis, we aimed to apply a model-based approach to evaluate cardiac monitoring protocols during trastuzumab treatment. This was done by simulating individual LVEF responses as induced by adjuvant treatment with trastuzumab in a virtual patient population, using the previously developed PK-PD model. The impact of cardiac monitoring protocols was incorporated into this framework, allowing evaluation of the impact of treatment interventions (e.g. dose termination or interruption) on outcome measures related to efficacy and toxicity, with respect to a particular monitoring protocol.

The PK-PD model that was used for this framework was developed using a cohort of unselected 'real-life' breast cancer patients (12). However, since we are applying this model for predictive purposes, we also aimed to further qualify the developed PK-PD model using recently reported data in literature, for its intended application (6).

Objectives

The objectives of this analysis were to evaluate the currently used cardiac monitoring strategy, and to suggest further improvements in cardiac monitoring strategies by inclusion of adaptive properties to the current monitoring protocol. Furthermore, we aimed to demonstrate how a model-based framework can be used to evaluate repeated measurement (cardiac) monitoring protocols.

MATERIALS AND METHODS

Software

This analysis was conducted using the scripting language R (version 2.12) (16). PK-PD models were simulated using the differential equation solver-package deSolve (17).

External Evaluation of the Developed PK-PD Model

Slamon *et al.* (6) described a randomized clinical trial investigating the adjuvant treatment with trastuzumab. One of the study arms contained patients treated with docetaxel and carboplatin together with 52 weeks of trastuzumab treatment, whereas in another arm patients received a anthracycline-containing regimen prior to trastuzumab treatment. Docetaxel and carboplatin, which were also part of the treatment arms including (cardiotoxic) anthracyclines and trastuzumab, where assumed not to affect the LVEF to relevant extent. To our knowledge, no convincing reports are available of cardiotoxic effects of docetaxel or carboplatin either alone or as combination treatment, which is also supported by the lack of any dosing adjustments in the treatment guidelines for these drugs.

In order to perform an external qualification of the previously developed PK-PD model between trastuzumab exposure and LVEF dynamics, we simulated 1000 LVEF profiles according to i) the trastuzumab dosing regimen reported in this trial, for the trastuzumab-only treatment arm, and ii) the treatment arm in which patients received prior anthracycline treatment. The reported (6) mean change in LVEF over time was digitized, and this change was scaled to the baseline LVEF value that was found in the previously described PK-PD model, to allow comparison between profiles. Subsequently, the mean and 10^{th} and 90^{th} percentiles of the simulated profiles were also computet and graphically depicted, to allow visual comparison.

Model Based Framework

The simulation framework comprised the following steps: i) simulate individual LVEF-time profiles using the developed PK/PD model; ii) apply treatment pausing or termination, according a cardiac monitoring protocol; iii) calculate outcome measures to assess the performance of the cardiac management protocol.

Simulation of Patient Characteristics

Throughout this analysis, body weight (WT) values were simulated stochastically to generate individual trastuzumab doses. WT was simulated from the distribution as was found in a typical clinical study population (12) (Table I).

Table I Simulation Characteristics of Body Weight, Used for Calculation of Individual Trastuzumab Doses

Description	Value
Mean body weight	70 kg
Standard deviation of body weight	12
Lower and upper truncation points	40–150 kg

Input-Output Model

The input-output model was a population PK-PD model that was used to stochastically simulate LVEF-time profiles, previously described by us (12). This model comprised an effect compartment model which is linked to an Emax-equation (parameterized in terms of EC_{50} and E_{max}) describing the relationship between the effect compartment concentration and the decline in LVEF. Thus, patients with a high sensitivity to develop cardiotoxicity will have lower EC_{50} values. Inter-individual variability was present on baseline LVEF, EC_{50} and the recovery half-life ($T_{1/2rec}$). With respect to all monitoring protocol simulations, baseline LVEF values were re-sampled if baseline LVEF values of <50% were obtained prior to start of simulation, since only patients with a LVEF>50% were considered eligible for trastuzumab treatment.

Monitoring Execution Model

For each scenario, individual LVEF profiles were simulated. The SPC-defined three-weekly dosing regimen was used for all simulations, i.e. using a loading dose of 8 mg/kg and maintenance dose of 6 mg/kg. The standard time points of LVEF evaluation moments were at t=0, 3, 6 and 9 months. Profiles were re-simulated each time the protocol under evaluation indicated a dose intervention.

For each evaluated monitoring scenario, 20.000 individual LVEF profiles were sampled 200 times from a distribution of 100.000 simulated LVEF profiles. Re-sampling was performed in order to quantify uncertainty for the evaluation metrics. The large number of 20.000 simulations was chosen to obtain a reliable representation of the relatively infrequently occurring cardiac events. An exploratory simulation was conducted evaluating the relationship between the number of simulations and the variance of the distribution of mean AUC_{45} values >0 (see next paragraph for AUC_{45} definition). At a number of 20.000 simulations the mean AUC_{45} distribution appeared to stabilize around a relatively precise estimate (5.1 CV%) (Fig. 1), while still being also computationally feasible.

Evaluation Metrics

Cardiotoxicity was quantified using the $AUC_{<45}$, which was defined as the area below a LVEF threshold of 45%, and above the LVEF-time curve, as has been illustrated in Fig. 2. The $AUC_{<45}$ takes into account the magnitude of (potential) cardiotoxicity both in terms of duration and severity. Since the LVEF is unitless, the unit of $AUC_{<45}$ was defined as 'LVEF45 days'.

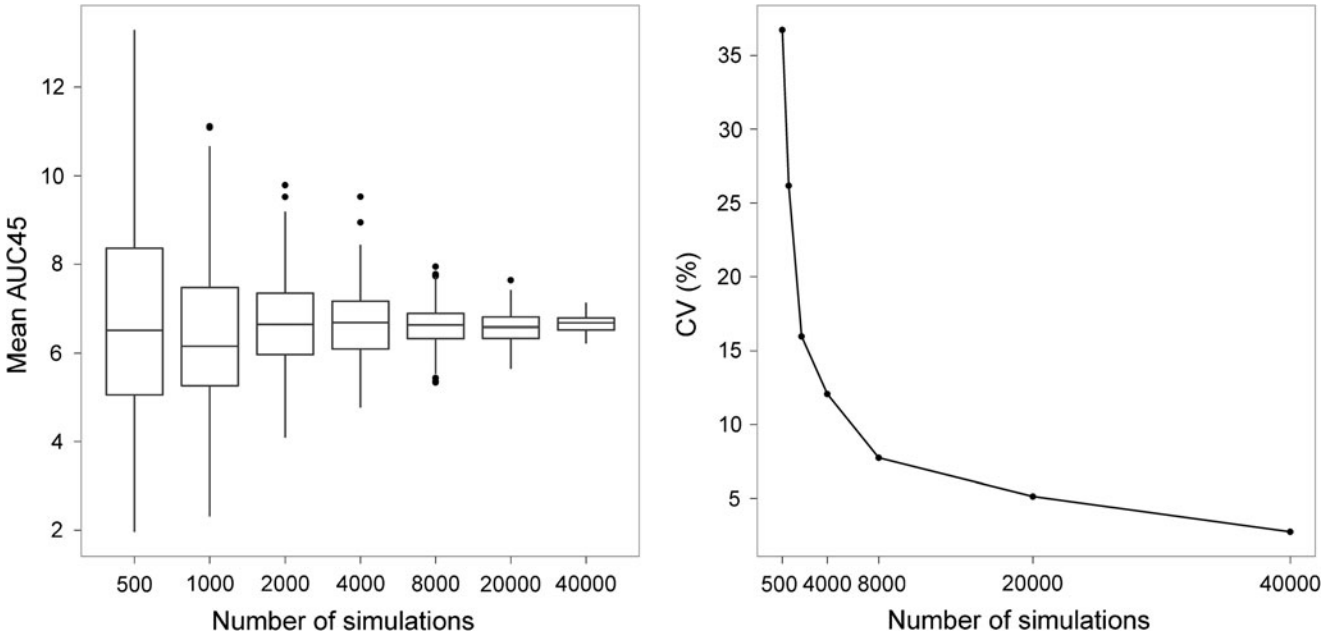

Fig. 1 Distribution of simulated mean AUC_{45} values for $AUC_{45} > 0$ (*left*), and the associated coefficients of variation (CV%) (*right*), for different numbers of patients in one simulation dataset, to support selection of the appropriate size of simulation datasets. The solid line represents the median, the areas are the 25^{th} and 75^{th} percentiles.

The LVEF threshold of 45% was chosen based on the associated risk for cardiac death for LVEF values below 35%(18), while taking into account a safety margin of 10%. This safety margin was based on the observed uncertainty in LVEF measurements of 9.11 CV% as was quantified earlier (12). In addition to this rationale, the selected 45% threshold can also be considered to be supported by the currently used SPC-protocol, which was used throughout the clinical development of trastuzumab. The SPC-protocol is based on a >10% drop in LVEF together with a LVEF below 50%. Thus, on average, this also leads to a LVEF threshold of 45%.

A metric for the risk of developing cardiotoxicity was defined by simulation of a full-treatment (FT) scenario. Here, LVEF-time profiles for a full trastuzumab treatment of one year were generated, without any dose or schedule adjustments. Based on the resulting $AUC_{<45}$ values, patients were classified according to their (hypothetical) full-treatment $AUC_{<45}$ (FT-AUC_{45}), between either having no risk ($AUC_{<45}$=0 LVEF45 days) to having a severe risk ($AUC_{<45}$>45 LVEF45 days) of cardiotoxicity.

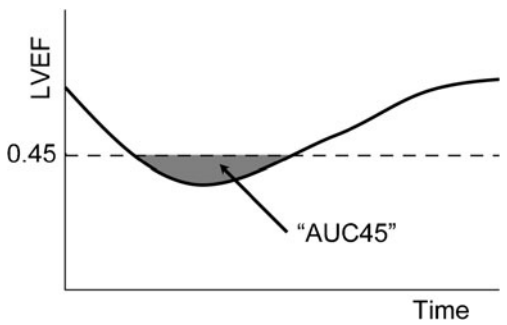

Fig. 2 Illustration of the AUC_{45} metric used to quantify cardiac toxicity.

Using above definitions, the following protocol evaluation metrics were defined: i) dose intensity, as measure of treatment efficacy, ii) observed $AUC_{<45}$ (O-AUC_{45}), as measure of cardiotoxicity, iii) reduction in $AUC_{<45}$ compared to full treatment $AUC_{<45}$, as measure of protocol intervention effectiveness, and iv) the number of LVEF measurements per patient, as measure of monitoring burden for the patient.

Dose intensity was calculated using the ratio between the received number of doses and the full number of possible doses. Dose-intensity distributions were graphically depicted for each simulation scenario, and were stratified by the aforementioned full-treatment risk categorization.

The reduction in $AUC_{<45}$ compared to FT-AUC_{45} was used as a measure of protocol intervention effectiveness. The magnitude of success S of a dose reduction in patients at risk for experiencing cardiotoxicity (i.e. with FT-AUC_{45}>0), was defined as magnitude of change in the O-AUC_{45} compared to the FT-AUC_{45}, as defined below.

$$S = \left(\frac{FT\text{-}AUC_{45} - O\text{-}AUC_{45}}{FT\text{-}AUC_{45}} \right) \times 100$$

Finally, for each of the described evaluation metrics, the median and inter-quartile range (IQR) were computed from the 200 resampled datasets containing 20.000 simulations each as described earlier.

Simulation Scenarios of Monitoring Protocols

In this work, we have evaluated three main scenarios for monitoring protocols.

Scenario S1 represents the currently used SPC-based monitoring protocol, and is schematically depicted in Fig. 3a. We also propose two alternative monitoring protocols, which are still based on the SPC, but include adaptive features.

Scenario S2 (Fig. 3b) is based on the exclusion of low-risk patients. For instance, patients with very high baseline LVEF values could be considered to have a negligible risk for experiencing cardiac toxicity, and might not benefit from the 3-monthly monitoring. Therefore, in this scenario the SPC protocol was extended with an exclusion rule based on high (i.e. low-risk) LVEF baseline values.

Scenario S3 (Fig. 3c) also includes the exclusion of low-risk patients from scenario S2, but an optimized criterion was defined to identify patients at risk for cardiotoxicity. In this scenario, a score of 1 point each wass assigned for either experiencing a LVEF decrease >10%, or, experiencing an absolute LVEF<45%, after each LVEF evaluation. If either of these two events occurs, the LVEF is re-evaluated before the next dosing event (i.e. similar to the SPC-based protocol). If a patient reaches a cumulative stopping score, the trastuzumab treatment is terminated. Different cumulative scores were evaluated. The rationale for the S3 scenario is as follows. In agreement with the SPC protocol, either absolute lowered LVEF values or substantial declines in LVEF are considered to be indicative of (potential) cardiotoxicity. The SPC-based protocol, however, only considers cardiac toxicity when both LVEF<50%, and the LVEF decrease from baseline >10%, ignoring cases where only one of these events occurred. For instance, a patient may have a consistently decreased LVEF (i.e. below or around 45%), but may still not experience the minimum change in LVEF from baseline required to qualify as cardiac event.

RESULTS

External Evaluation of the Developed PK-PD Model

We compared the PK-PD model predictions of our previously developed model (12) with recently published external data (6) regarding the change in LVEF. The visual comparison between the observed LVEF profiles in patients treated

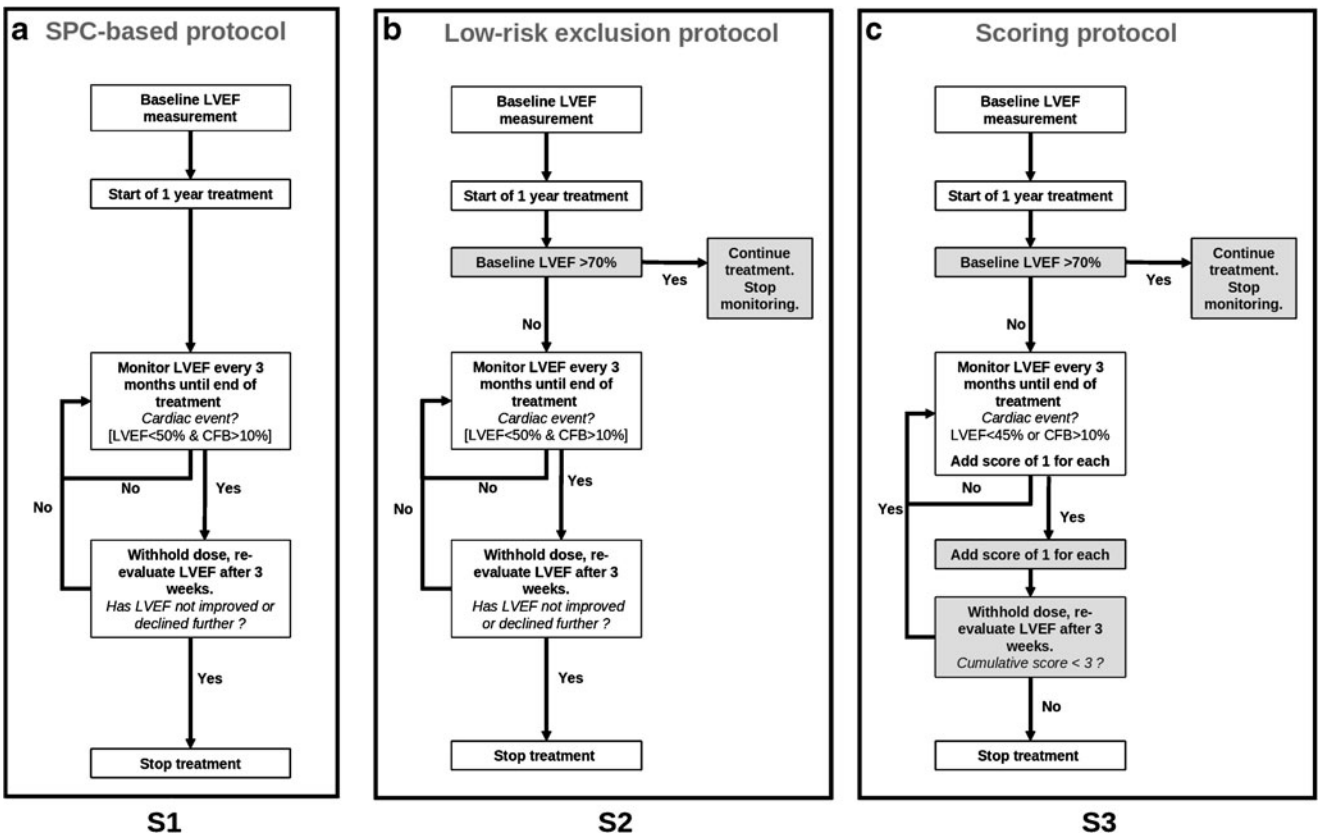

Fig. 3 Schematic representation of the SPC-protocol (**a**), the adaptive protocol (**b**), and the scoring-based protocol (**c**). Gray areas represent differences between the SPC-based protocol.

with adjuvant trastuzumab treatment together with the model simulated profiles for the applied dosing regimen are depicted in Fig. 4. The mean change in LVEF during treatment was found to overlap adequately with the PK-PD model simulated change, although the decline was slightly less in the external observed dataset, but nontheless supporting this PK-PD model for application in the model-based evaluation of cardiac monitoring protocols.

Evaluation of Cardiac Monitoring Protocols

In Tables I to IV, the results of the evaluation with respect to the predefined evaluation metrics are defined, while Fig. 5 provides a graphical overview of the differences between monitoring protocols S1 to S3.

Selection of the Low-Risk Exclusion Cut-off Threshold

For the cut-off levels for scenario S2 (low-risk exclusion) we selected a cut-off threshold of >70% for the full evaluation, based on exploratory simulations using different cut-off levels between LVEF values of 60 to 80% (Fig. 6). The cut-off level of >70% was expected to lead to a negligible amount of patients experiencing cardiotoxicity (e.g. $AUC_{45}>0$), while still selecting a substantial number of patients.

Cumulative Stopping Scores for the Scoring Protocols

For scenario S3 (scoring protocol), we evaluated cumulative stopping scores of 2, 3 and 4, of which the results are all included in Table II to IV. Differences in evaluation metrics

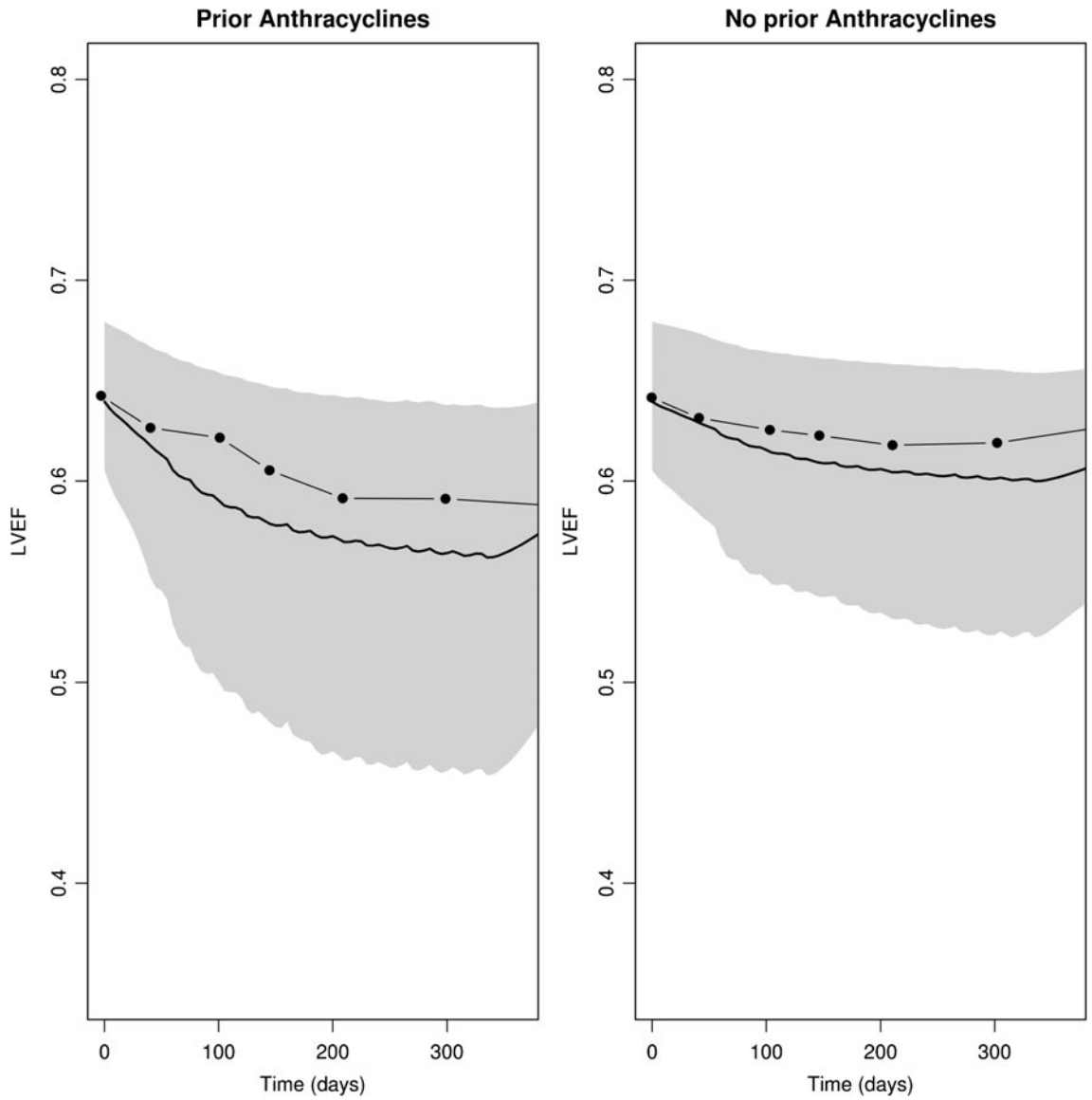

Fig. 4 Mean LVEF *versus* time (days) as reported by Slamon *et al.* (6) (*solid circles*) *versus* model predictions by van Hasselt *et al.* (12) (*black solid line*), for patients who received prior anthracyclines and without receiving prior anthracyclines. The gray area represents the model predicted 90% prediction interval.

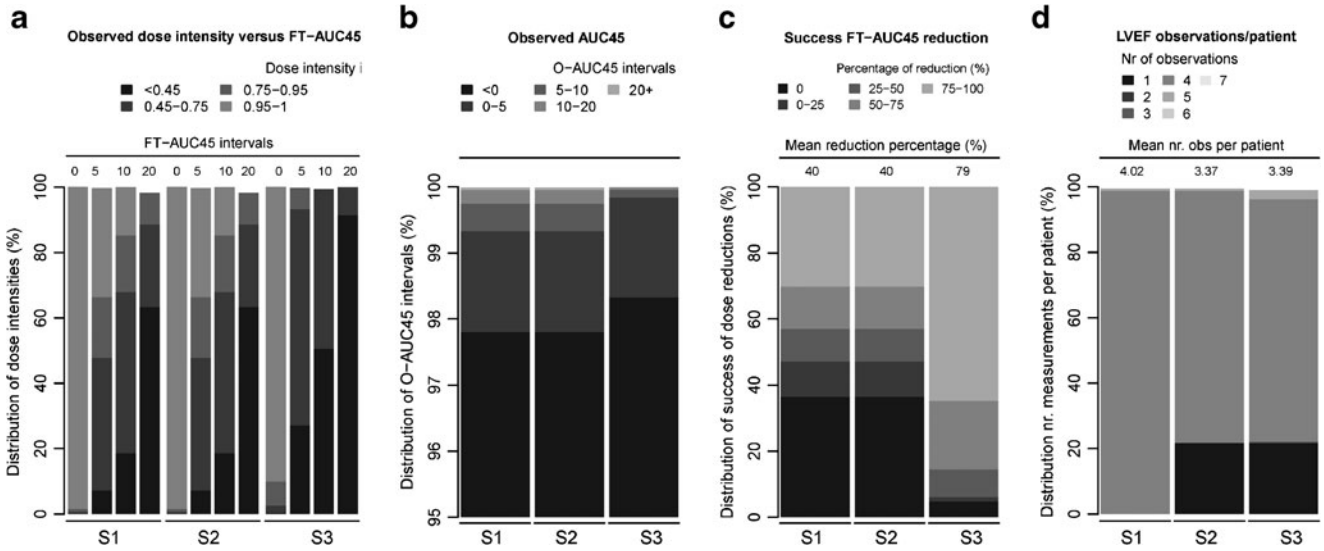

Fig. 5 Simulation based evaluation of the SPC-protocol (S1), exclusion of low-risk patients with LVEF > 70% (S2), and the scoring-based protocol (S3) with a cumulative stopping score of 3 points. Evaluation was performed based on the distribution of dose intensities for different FT-AUC$_{45}$ intervals (**a**), the observed AUC$_{45}$ distribution (**b**), the success of the percentage of FT-AUC$_{45}$ reduction (**c**), and the number of observations per patient (**d**). The depicted values represent the median evaluation metric values obtained from 20.000 simulations which were resampled 200 times.

for different stopping scores were not remarkably large. Further throughout this manuscript, we will discuss scenario S3 based on a cumulative stopping score of 3. This was selected as intermediate measure between a more conservative monitoring strategy (i.e. stopping score is 2) or a strategy in which relatively more toxicity was considered acceptable.

Dose Intensity

In Table II, and schematically in Fig. 5a, the results of the dose intensity evaluation are depicted. Scenarios S1 and S2 were similar since these two scenarios are equivalent except for exclusion of low-risk patients, who did not experience any cardiac toxicity (i.e. LVEF < 45%). For scenario S3 it is clear that patients not experiencing cardiac toxicity receive marginally higher dose intensities than patients in S1/S2 (i.e. SPC), while patients with serious cardiac toxicity (i.e. high AUC$_{<45}$ levels) receive substantially lower dose intensities.

Observed AUC$_{45}$ Distribution

For each scenario the O-AUC$_{45}$ distribution was used to to quantify the number of patients with potential cardiac damage. In Table III, and schematically in Fig. 5b, the results of this evaluation are depicted. Again, S1 and S2 were equivalent. For S3, a favorable distribution of O-AUC$_{45}$ values was predicted, substantially reducing the number of patients with high O-AUC$_{45}$ levels.

Dose-Reduction Success Compared to Full Treatment AUC$_{45}$

The success of dose reductions as implemented by each protocol is depicted in Table IV and schematically in Fig. 5c. While in scenario S1/S2, the mean success of the dose reduction percentage was 40%, scenario S3 was shown to be substantially more effective in dose interventions for patients at risk for cardiac toxicity, with a mean success percentage of 79%.

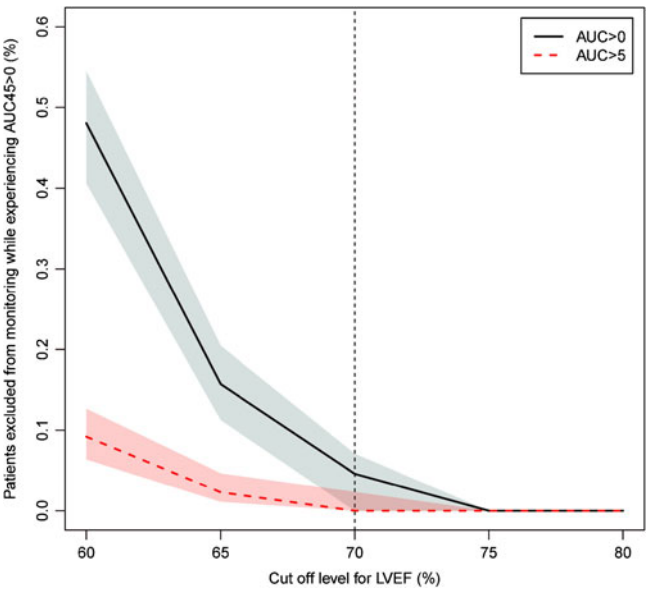

Fig. 6 Simulated percentage of patients (%) incorrectly excluded from monitoring while still experiencing AUC$_{45}$ > 0 (black solid line) or AUC$_{45}$ > 5 (red dashed line), for different cut-off levels. The areas are the 25th and 75th percentiles.

Table II Percentage of Patients by Dose Intensity Interval for Different FT-AUC_{45} Intervals and for Different Evaluated Monitoring Protocols

Monitoring protocol	Dose intensity interval	Percentage of patients (%) (median, IQR)			
		FT- AUC_{45} 0–5	*FT-AUC_{45} 5–10*	*FT- AUC_{45} 10–20*	*FT- AUC_{45} >20*
S1 (SPC)	0.00–0.45	0.05 (0.04–0.06)	7.18 (5.5–8.89)	18.57 (16.4–21.36)	63.33 (58.33–67.52)
	0.45–0.75	0.62 (0.59–0.65)	40.48 (37.69–43.66)	49.36 (45.15–52.05)	25.29 (21.62–29.73)
	0.75–0.95	0.87 (0.83–0.91)	18.72 (16.07–21.05)	17.28 (15.05–20)	9.72 (6.45–13.89)
	0.95–1.00	98.46 (98.41–98.51)	33.33 (30.53–36.58)	14.67 (12.5–16.94)	<0.01 (0–2.78)
S2 (Low-risk exclusion)	0.00–0.45	0.05 (0.04–0.06)	7.18 (5.5–8.89)	18.57 (16.4–21.36)	63.33 (58.33–67.52)
	0.45–0.75	0.62 (0.59–0.65)	40.48 (37.69–43.66)	49.36 (45.15–52.05)	25.29 (21.62–29.73)
	0.75–0.95	0.87 (0.83–0.91)	18.72 (16.07–21.05)	17.28 (15.05–20)	9.72 (6.45–13.89)
	0.95–1.00	98.46 (98.41–98.51)	33.33 (30.53–36.58)	14.67 (12.5–16.94)	<0.01 (0–2.78)
S3 (Scoring, CSS=3)	0.00–0.45	0.28 (0.26–0.3)	27.13 (24.94–30)	50.65 (47.93–53.81)	91.43 (88.52–94.12)
	0.45–0.75	2.26 (2.2–2.33)	66.2 (62.63–69.09)	48.89 (45.68–52.07)	8.57 (5.88–11.48)
	0.75–0.95	7.39 (7.24–7.47)	6.53 (4.94–7.84)	<0.01 (<0.01–<0.01)	<0.01 (<0.01–<0.01)
	0.95–1.00	90.08 (89.95–90.21)	<0.01 (<0.01–<0.01)	<0.01 (<0.01–<0.01)	<0.01 (<0.01–<0.01)
S3 (Scoring, CSS=2)	0.00–0.45	0.8 (0.77–0.84)	34.88 (31.56–37.74)	55 (51.93–58.02)	91.43 (88.52–94.12)
	0.45–0.75	3.27 (3.2–3.35)	61.41 (57.97–64.76)	44.78 (41.94–48.07)	8.57 (5.88–11.48)
	0.75–0.95	5.83 (5.72–5.93)	3.37 (2.51–4.72)	<0.01 (<0.01–<0.01)	<0.01 (<0.01–<0.01)
	0.95–1.00	90.08 (89.95–90.21)	<0.01 (<0.01–<0.01)	<0.01 (<0.01–<0.01)	<0.01 (<0.01–<0.01)
S3 (Scoring, CSS=4)	0.00–0.45	0.21 (0.2–0.23)	16.9 (15.33–19.4)	41.06 (37.66–44.29)	91.43 (88.52–94.12)
	0.45–0.75	1.86 (1.79–1.92)	71.8 (68.73–73.86)	58.23 (55.38–61.87)	8.57 (5.88–11.48)
	0.75–0.95	7.85 (7.74–7.95)	10.75 (9.38–12.66)	<0.01 (<0.01–<0.01)	<0.01 (<0.01–<0.01)
	0.95–1.00	90.08 (89.95–90.21)	<0.01 (<0.01–<0.01)	<0.01 (<0.01–<0.01)	<0.01 (<0.01–<0.01)

SPC Summary of protocol characteristics (monitoring protocol); *CSS* Cumulative stopping score; *FT-AUC_{45}* Full treatment AUC_{45}; *IQR* Inter-quartile range

Burden of Monitoring

The distribution of the number of LVEF measurements was also evaluated, to assess the overall burden for patients (Table V, Fig. 5d). The highest number of LVEF observations per patient was observed for the SPC (S1), with a mean value of 4.02 observations per patient. This figure was substantially reduced by excluding patients with baseline LVEF values >70%, to a mean value of 3.37 observations per patient. For scenario S3, the mean value was 3.39 observations per patient. Although slightly higher than S2, this number was still substantially lower than for the SPC (S1) scenario.

DISCUSSION

We demonstrated how a model-based approach can be used to quantitatively evaluate cardiac monitoring protocols during the adjuvant treatment with trastuzumab. The proposed adaptations to the currently used SPC-based monitoring protocol appear to be beneficial since the number of LVEF

Table III Percentage (Median, IQR) of Patients Present In O-AUC_{45} Strata for Different Monitoring Protocols

Monitoring protocol	Percentage (%) (median, IQR)				
	O-AUC_{45} <0	*O-AUC_{45} 0–5*	*O-AUC_{45} 5–10*	*O-AUC_{45} 10–20*	*O-AUC_{45} >20*
S1 (SPC)	97.8 (97.76–97.88)	1.52 (1.47–1.57)	0.42 (0.39–0.44)	0.21 (0.19–0.23)	0.03 (0.03–0.04)
S2 (Low-risk exclusion)	97.8 (97.76–97.88)	1.52 (1.47–1.57)	0.42 (0.39–0.44)	0.21 (0.19–0.23)	0.03 (0.03–0.04)
S3 (Scoring, CSS=3)	98.33 (98.28–98.39)	1.51 (1.46–1.56)	0.12 (0.11–0.14)	0.03 (0.02–0.03)	<0.01 (<0.01–<0.01)
S3 (Scoring, CSS=2)	98.39 (98.33–98.44)	1.47 (1.42–1.51)	0.12 (0.1–0.13)	0.03 (0.02–0.03)	<0.01 (<0.01–<0.01)
S3 (Scoring, CSS=4)	98.27 (98.22–98.33)	1.54 (1.5–1.6)	0.14 (0.13–0.16)	0.03 (0.02–0.04)	<0.01 (<0.01–<0.01)

SPC Summary of protocol characteristics (monitoring protocol); *CSS* Cumulative stopping score; *IQR* Inter-quartile range; *O-AUC_{45}* Observed AUC_{45}

Table IV Success of FT-AUC_{45} Reduction (%) for Different Monitoring Protocols, Depicted as the Percentage (%, Median, IQR) of Patients Present in Different Strata for the Success of FT-AUC_{45} Reduction, and the Mean FT-AUC_{45} Reduction (Median, IQR)

Monitoring protocol	Success of FT-AUC_{45} reduction (%)	Percentage of patients (%) (median, IQR)	Mean FT-AUC_{45} reduction (%) (median, IQR)
S1 (SPC)	0–25	36.45 (36.45–36.45)	40.0 (39.0–41.1)
	25–50	10.69 (10.69–10.69)	
	50–75	9.92 (9.92–9.92)	
	75–100	12.79 (12.79–12.79)	
	100	30.15 (30.15–30.15)	
S2 (Low-risk exclusion)	0–25	36.45 (36.45–36.45)	40.0 (39.0–41.1)
	25–50	10.69 (10.69–10.69)	
	50–75	9.92 (9.92–9.92)	
	75–100	12.79 (12.79–12.79)	
	100	30.15 (30.15–30.15)	
S3 (Scoring, CSS=3)	0–25	4.77 (4.77–4.77)	79.0 (78.4–79.73)
	25–50	1.34 (1.34–1.34)	
	50–75	8.40 (8.40–8.40)	
	75–100	20.8 (20.80–20.80)	
	100	64.69 (64.69–64.69)	
S3 (Scoring, CSS=2)	0–25	4.77 (4.77–4.77)	80.2 (79.6–81.0)
	25–50	1.15 (1.15–1.15)	
	50–75	7.25 (7.25–7.25)	
	75–100	20.04 (20.04–20.04)	
	100	66.79 (66.79–66.79)	
S3 (Scoring, CSS=4)	0–25	4.77 (4.77–4.77)	77.6 (76.88–78.3)
	25–50	1.34 (1.34–1.34)	
	50–75	9.92 (9.92–9.92)	
	75–100	22.90 (22.90–22.90)	
	100	61.07 (61.07–61.07)	

SPC Summary of protocol characteristics (monitoring protocol); CSS Cumulative stopping score; IQR Inter-quartile range; FT-AUC45 Full treatment AUC_{45}

observations is decreased (S2), and the overall amount of cardiac damage is reduced (i.e. $AUC_{<45}$, S3) while retaining a high dose intensity in patients with no clinically relevant LVEF decline.

External Evaluation of the Developed PK-PD Model

The developed PK-PD model demonstrated adequate predictions of the change in LVEF in response to trastuzumab, based on the external evaluation that was conducted (Fig. 4). The magnitude of mean decline as described in the external dataset was slightly less then the simulated mean change. This could be related to the study population included in the model-building dataset, which consisted of a real-life cohort including patients with health states that would not have been included in the controlled clinical trial setting described by Slamon *et al.*, but is nonetheless more representative of the actual situation in routine patient care. Nonetheless, this indicated that the developed PK-PD model was qualified for the intended application to perform a model-based evaluation of monitoring protocols. In the evaluated treatment arm of the external study, docetaxel and carboplatin were co-administered together with trastuzumab. We do not expect that this will have any relevant impact on the reported LVEF, since there have been no reports of cardiotoxic effects of these drugs.

Evaluation of Cardiac Monitoring Protocols

It was shown that patients who have no LVEF below 45% (i.e. the O-AUC_{45} is 0) in the SPC-based protocols (i.e. S1/S2) generally receive the full treatment (0.95–1 dose intensity in 98.46% of patients), while for scenario S3, 7.39% of patients are assigned to have a mild dose reduction (0.75–0.95 dose intensity), which should not have been necessary for this patient group (Fig. 5a, Table II). The clinical implications of this limited dose reduction is difficult to assess because it is not known how dose intensity relates to efficacy, but it is an important limitation of the scoring protocol that should be considered when interpreting these results.

However, patients with serious risk for cardiac toxicity (e.g. high FT-AUC_{45}), received substantially higher dose reductions in scenario S3, compared to the SPC-based protocol (i.e. S1/S2). We consider this an important advantage of the S3

monitoring strategy. The appropriateness of dose reductions suggested by S3 is further supported based on the observed $AUC_{<45}$ distribution (Fig. 5b, Table III) and the success of dose reduction evaluation (Fig. 5c, Table IV). The exclusion of low-risk patients with a LVEF >70% was considered appropriate.

This risk stratification strategy resulted in a substantial reduction of the number of LVEF measurements (from 4.02 to 3.37 observations per patient) (Fig. 5d, Table V). The number of LVEF measurements for S3 is only slightly increased compared to scenario S2.

We consider the predicted reduction in number of observations compared to S1 (i.e. SPC-schedule) to be an important improvement. The burden and costs of MUGA scans or echography measurements typically used for obtaining LVEF measurements cannot be ignored, and should only be performed if this is relevant for the patient. Moreover, the scoring-based protocol S3 was predicted to be more effective in identifying patients with high $AUC_{<45}$ values compared to the SPC, while needing a reduced mean number of LVEF observations per patient.

Even though there are some clear advantages of the proposed changes to the SPC protocol, the choice for any monitoring protocol will always be centered around defining a clinically acceptable balance between safety, efficacy (i.e. dose intensity), and burden of monitoring. Monitoring schedules with more frequent monitoring will obviously lead to adequate detection of cardiac toxicity, but will impose also a potentially unacceptable burden on patients. The quantitative insight of the current evaluation can however be used as a tool for rationally comparison of potential monitoring strategies by clinicians. Further understanding of the ultimate clinical implications of changes in LVEF caused by trastuzumab treatment to support further selection of the most appropriate monitoring schedule.

Table V Number of LVEF Observations Per Patient During Treatment for Different Monitoring Protocols, Depicted as the Percentage (%, Median, IQR) of Observations for Each Number of Observations, and the Mean Number of Observations (Median, IQR)

Protocol	Number of observations	Percentage (%) (median, IQR)	Mean number observations (median, IQR)
S1 (SPC)	1	NA	4.02 (4.02–4.02)
	3	NA	
	4	98.84 (98.8–98.88)	
	5	0.66 (0.62–0.7)	
	6	0.46 (0.44–0.49)	
	7	0.03 (0.02–0.04)	
S2 (Low-risk exclusion)	1	21.72 (21.55–21.89)	3.37 (3.36–3.37)
	3	NA	
	4	77.14 (76.96–77.33)	
	5	0.64 (0.61–0.68)	
	6	0.46 (0.44–0.48)	
	7	0.03 (0.02–0.04)	
S3 (Scoring, CSS=3)	1	21.72 (21.55–21.89)	3.39 (3.39–3.4)
	3	0.47 (0.44–0.50)	
	4	74.08 (73.85–74.25)	
	5	2.85 (2.79–2.92)	
	6	0.9 (0.86–0.93)	
	7	NA	
S3 (Scoring, CSS=2)	1	21.72 (21.55–21.89)	3.37 (3.36–3.37)
	3	0.46 (0.44–0.49)	
	4	75.6 (75.41–75.78)	
	5	2.21 (2.15–2.28)	
	6	NA	
	7	NA	
S3 (Scoring, CSS=4)	1	21.72 (21.55–21.89)	3.41 (3.41–3.42)
	3	0.40 (0.37–0.42)	
	4	73.28 (73.06–73.48)	
	5	2.76 (2.69–2.83)	
	6	1.54 (1.5–1.6)	
	7	0.32 (0.29–0.34)	

SPC Summary of protocol characteristics (monitoring protocol); CSS Cumulative stopping score; IQR Inter-quartile range; NA Not available

Rational for the Scoring-Based Protocol

The scoring-based protocol S3 was based on the occurrence of two important risk factors for cardiac toxicity, namely, a LVEF below 45%, which is associated with sudden cardiac death, or, a substantial decline in LVEF, which is considered to be an important risk factor for experiencing a low LVEF level before the next monitoring event. However, because of the measurement error associated with individual LVEF measurements, we incorporated a cumulative stopping score in order to limit incorrect termination of the treatment. Increasing the cumulative stopping score will lead a setting in which more toxicity is accepted, whereas decreasing it will lead to a more conservative monitoring protocol.

Metastatic Breast Cancer

We specifically focused on the treatment of adjuvant breast cancer, since these patients, who have the potential to be cured, will have the greatest benefit from preserving cardiac function while optimizing dose intensity when this is safe to do. For metastatic breast cancer (MBC), treatment durations are typically based on the nature of disease progression, which makes dose intensity a less relevant evaluation metric. Nonetheless, we consider the proposed strategies also relevant for monitoring of treatment in patients with MBC.

Evaluation Metrics

Different evaluation metrics for cardiac toxicity or cardiac events have been reported in literature (19). In the current evaluation, an LVEF threshold of 45% has been used as level for risk of cardiotoxicity. In previous studies, levels between 35% have been associated with an increased risk of cardiac death (18). Especially given the nature of the investigated patient group (patients with primary non-metastasized breast cancer) we have considered a safety margin of 10%, thus leading to a threshold of 45%. The associated metric of $AUC_{<45}$ was considered most appropriate, as this takes into account both the absolute LVEF value, as well as the time below a certain threshold.

Model-Based Framework

The model-based evaluation approach applied in this analysis allowed for *in silico* evaluation of different cardiac monitoring scenarios. Although we acknowledge that ultimately improvements in monitoring schedules should be evaluated in prospective clinical studies, this model-based approach allowed for *a priori* optimization of optimized monitoring protocols, which would not have been feasible to perform via other (clinical-trial based) strategies in our view.

The outcome of this analysis is driven by the input-output model that describes the relationship between trastuzumab exposure and LVEF decline, and the performance of this model is therefore pivotal. Using an external evaluation we provided more confidence in the developed model, since the model adequately described this external clinical study.

We consider the applied approach of a model-based framework comprising both exposure-response characteristics as well as clinical decision making rules to be also relevant for other scenarios in which the safety of a pharmacological intervention is monitored using repeated measurements of safety biomarkers.

Anthracycline Pretreatment

In the previously developed model (12) we identified that patients pretreated with prior anthracyclines had increased sensitivity (lower EC_{50}) for development of cardiac toxicity (e.g. the magnitude of LVEF decline was increased). However, in the current analysis we did not explicitly simulated patients who received anthracycline pretreatment. Therefore, this analysis can not provide quantitative insight in the distribution of evaluation metrics for this specific cohort of patients. Nonetheless, also patients who are anthracycline pretreatment naïve can have increased sensitivity to cardiac toxicity, and these were as such included in the current simulation in adequate amounts because of the large number of simulations performed.

We still anticipate that the low-risk exclusion protocol S2 with a threshold of 70% will be appropriate for patients with anthracycline pretreatment, because sensitive patients without anthracycline pretreatments were present also in the current simulation study, and the incidence of serious cardiac toxicity ($AUC_{45}>5$) was found negligible in this subgroup. However as a safety precaution, exclusion, or an increased LVEF exclusion threshold for anthracycline pretreated patients from the S2 low-risk exclusion monitoring protocol could also be considered.

The scoring-based monitoring protocol S3 has shown to have increased performance with respect to reducing the dose for patients with more serious cardiac toxicity (e.g. higher FT-AUC_{45}), which is expected in patients with anthracycline pretreatment. Therefore the scoring-based monitoring protocol S3 is also considered appropriate for this specific patient group (potentially excluding low-risk exclusion of patients, as discussed above).

Cardiac Function Markers

Currently, the LVEF is still the main metric in use to monitor cardiac dysfunction and to adjust trastuzumab treatment if necessary. However, it would be useful if also other cardiac function evaluation metrics are further developed and applied,

in order to monitor trastuzumab associated cardiotoxicity and comparable cardiotoxic agents. Other imaging-based cardiac function markers, which are already available when perform echography or MUGA-scans for obtaining the LVEF, such as end-diastolic volume, could for instance also be considered (20,21). Biochemical markers such as NT-proBNP or troponines (22,23) could also be investigated further, and possibly used in conjunction with the LVEF to guide clinical decision making.

CONCLUSION

A model-based evaluation was used successfully to evaluate the current SPC-based cardiac monitoring protocol, and to propose and to define two alternative and potentially improved monitoring protocols. Adaptive monitoring protocols that allow selective monitoring based on exclusion of low-risk patients showed equal performance compared to the SPC, while decreasing the mean number of LVEF measurements needed. Using a scoring-based protocol, substantial improvements in the identification of patients with cardiac toxicity appear to be feasible. In conclusion, these optimized scenarios S2 and S3 both provide substantial benefit to the safe and effective treatment of patients with trastuzumab, and should be evaluated in prospective clinical studies to further support their application in clinical practice. Finally, the demonstrated approach may potentially also be useful for quantitative evaluation of monitoring schedules of other longitudinally collected drug toxicity or safety markers.

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