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Decisions on Further Research for Predictive Biomarkers of High-Dose Alkylating Chemotherapy in Triple-Negative Breast Cancer: A Value of Information Analysis

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ABSTRACT

Objectives: To inform decisions about the design and priority of further studies of emerging predictive biomarkers of high-dose alkylating chemotherapy (HDAC) in triple-negative breast cancer (TNBC) using value-of-information analysis. **Methods:** A state transition model compared treating women with TNBC with current clinical practice and four biomarker strategies to personalize HDAC: 1) BRCA1-like profile by array comparative genomic hybridization (aCGH) testing; 2) BRCA1-like profile by multiplex ligation-dependent probe amplification (MLPA) testing; 3) strategy 1 followed by X-inactive specific transcript gene (XIST) and tumor suppressor p53 binding protein (53BP1) testing; and 4) strategy 2 followed by XIST and 53BP1 testing, from a Dutch societal perspective and a 20-year time horizon. Input data came from literature and expert opinions. We assessed the expected value of partial perfect information, the expected value of sample information, and the expected net benefit of sampling for potential ancillary studies of an ongoing randomized controlled trial (RCT; NCT01057069). **Results:** The expected value of partial perfect information indicated that further research should be prioritized to the parameter group including "biomarkers' prevalence, positive predictive value (PPV), and treatment response rates (TRRs) in biomarker-negative patients and patients with TNBC" (€639 million), followed by utilities (€48 million), costs (€40 million), and transition probabilities (TPs) (€30 million). By setting up four ancillary studies to the ongoing RCT, data on 1) TP and MLPA prevalence, PPV, and TRR; 2) aCGH and aCGH/MLPA plus XIST and 53BP1 prevalence, PPV, and TRR; 3) utilities; and 4) costs could be simultaneously collected (optimal size = 3000). **Conclusions:** Further research on predictive biomarkers for HDAC should focus on gathering data on TPs, prevalence, PPV, TRRs, utilities, and costs from the four ancillary studies to the ongoing RCT.

Keywords: decision modeling, diagnostics, high-dose alkylating chemotherapy, predictive biomarkers, value of information.

Introduction

Triple-negative breast cancer (TNBC) accounts for 15% to 20% of newly diagnosed breast cancer cases [1]. At present, no targeted treatment exists for this subtype, and standard chemotherapy is the guideline-recommended treatment [2–5]. Although standard chemotherapy can be effective, 40% of patients with TNBC suffer from early relapses and have short postrecurrence survival [6,7]. Although second- and third-line treatments exist, these typically increase overall costs but do not contribute sufficiently to improve long-term health outcomes [8–10]. Therefore, improving first-line treatment seems a promising way forward to decrease both patient morbidity and health care costs in this population.

Because TNBC is a heterogeneous disease [11], treatment effectiveness could possibly be increased by basing its therapeutic management on subclassifications. Preclinical data [12–14], and clinical data from a retrospective study conducted alongside a prospective randomized controlled trial (RCT) in our center (the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital NKI) [15], indicate that high-dose alkylating chemotherapy (HDAC) may be an effective treatment option for TNBC tumors without functional BRCA1, also known as BRCA1-like tumors. Furthermore, in an extension of this study, it was found that by further characterizing BRCA1-like tumors with two other biomarkers, X-inactive specific transcript gene (XIST) [16] and tumor suppressor p53 binding protein (53BP1) [13,17,18], responses to HDAC treatment increase by 30%, that is, patients with a BRCA1-like

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profile, high expression of 53BP1 (53BP1+), and low expression of XIST (XIST−) have a 100% response rate compared with the 70% yielded with the BRCA1-like biomarker alone. On the basis of these results, a prospective RCT to test the survival advantage of treating TNBCs with the BRCA1-like biomarker and HDAC was started (Randomized phase II/III study of individualized neo-adjuvant chemotherapy in triple negative breast tumors [TNM trial, NCT01057069]). The trial started in 2010 and is currently ongoing.

As the research on BRCA1-like, XIST, and 53BP1 biomarkers is now progressing from initial clinical studies toward "pivotal" studies to determine their diagnostic, patient, and societal value, early-phase economic evaluation can be applied to improve the efficiency of the research and development process. Early-phase economic evaluations have a decision analytic approach to iteratively evaluate technologies in development so as to increase their return on investment as well as have better patient and societal impact when the technology becomes available [19]. For instance, value-of-information (VOI) methods quantify the potential benefit of additional information in the face of uncertainty. VOI is based on the idea that information is valuable because it reduces the expected costs of uncertainty surrounding a decision. A detailed explanation of the VOI methodology can be found elsewhere [20].

Because decisions on emerging technologies with scarce clinical studies will inevitably be uncertain, research is expected to be worthwhile but only up to a certain cost of research. VOI methods allow us to estimate an upper bound to the returns of further research expenditures and are particularly helpful in setting research priorities for specific model parameters as well as for specific research designs and sample sizes [21]. The data gathered in and the research infrastructure of the ongoing TNM trial provide an opportunity to reduce uncertainty in a range of parameters that inform the decision problem against additional costs. Therefore, this study aimed to identify for which specific ancillary study designs further research is most valuable, and to inform future decisions on emerging predictive biomarkers for the selection of HDAC for TNBC.

Methods

A Markov model was constructed with three mutually exclusive health states: disease-free survival (DFS), relapse (R) (including local, regional, and distant relapses), and death (D). Our analysis took a Dutch societal perspective and a time horizon of 20 years because the occurrence of relapses and deaths are expected within this time frame [6,22–24]. Effectiveness was assessed in terms of quality-adjusted life-years (QALY) and costs in 2013 euros (€). Future costs and effects were discounted to their present value by a rate of 4% and 1.5% per year, respectively [25].

Patient Population Studied and Strategies Compared

We modeled five identical cohorts of 40-year-old women with TNBC, four treated with personalized HDAC as dictated by biomarkers and one treated according to current practice, with a mean duration of 1 year (see Fig. 1 and description). Drug regimens were based on a published RCT comparing HDAC and standard chemotherapy efficacy in breast cancer [26].

1. BRCA1-like tested by array comparative genomic hybridization (BRCA1-like-aCGH): Women are initially tested for the BRCA1-like profile by aCGH. Those who have a BRCA1-like profile are assigned to the HDAC arm (4-FEC [fluorouracil, epirubicin, and cyclophosphamide], followed by 1-CTC [cyclophosphamide, thiotepa, and carboplatin]), and those missing the profile are assigned to standard chemotherapy (5-FEC).
2. BRCA1-like tested by multiplex ligation-dependent probe amplification (BRCA1-like-MLPA): MLPA was developed to be more time-efficient, cheaper, and technically less complicated than the aCGH [27]. We modeled this strategy exactly as the previous one.
3. BRCA1-like-aCGH followed by XIST and 53BP1 (BRCA1-like-aCGH/XIST-53BP1): Women are initially tested with the BRCA1-like-aCGH classifier, as aforementioned. Patients with a BRCA1-like profile are further tested for XIST and 53BP1 expression, and patients with a non–BRCA1-like profile receive standard chemotherapy. XIST expression is detected with an MLPA assay and 53BP1 by immunochemistry. These markers are interpreted together; patients with a BRCA1-like profile with a low expression of XIST and presence of 53BP1 are considered sensitive for HDAC and thus assigned to HDAC. Patients with any other combination of the markers are considered resistant and are assigned to standard chemotherapy.
4. BRCA1-like-MLPA followed by XIST and 53BP1 (BRCA1-like-MLPA/XIST-53BP1): This strategy was modeled exactly as the previous one, but by assessing the BRCA1-like status by MLPA.
5. Current clinical practice: All women are treated with standard chemotherapy.

Patients were classified as "respondents" to the assigned chemotherapy when no relapse occurred within the first 5 years and as "nonrespondents" in case such an event occurred within the first 5 years. This time frame was considered a reasonable limit to include all events related to chemotherapy response [6,7,28].

After the intervention, patients enter into the DFS health state of the model, in which they will remain for the first year, accruing the costs and the health-related quality-of-life (HRQOL) weights of the administered chemotherapy. During this year, patients can die from chemotherapy-related toxic events (septicemia and heart failure [26]) or from events not related to breast cancer. Patients can move to the R health state from the first year onward. Patients with a relapse receive treatment and can 1) remain in the R health state and accrue the costs and HRQOL weights of the DFS health state, representing a "cured" relapse, or 2) die from breast cancer or other unrelated cause. We assumed that patients could have only one relapse during the time horizon of the model.

Model Input Parameters

The baseline prevalence of BRCA1-like was derived from three patient series (n = 377) in our hospital [29], including patients enrolled in the TNM trial, and it was considered equal for both MLPA and aCGH tests. The baseline prevalence of BRCA1-like/XIST−/53BP1+ was determined from an existing retrospective study from a prospective RCT in our institute [15] (n = 60), separately for the MLPA and the aCGH tests. This patient series was also used to derive 1) the positive predictive value (PPV) (proportion of biomarker-positive patients responding to HDAC as determined by the MLPA and aCGH BRCA1-like tests alone, and by their combination with the XIST and the 53BP1 tests); 2) the treatment response rates (TRRs) of biomarker-negative patients as determined by the MLPA and aCGH BRCA1-like tests alone, and by their combination with the XIST and the 53BP1 tests; and 3) the TRRs of patients with TNBC.

The transition probabilities (TPs) of relapse-free survival and breast-cancer–specific survival were estimated from the study by Lester-Coll et al. [30], in turn derived from the survival data of Kennecke et al. [23]. Using these data required making the