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ORIGINAL ARTICLE

Using the analytic hierarchy process to elicit patient preference in the evaluation of first-line treatment of HER2-overexpressing metastatic breast cancer

Uso do processo analítico hierárquico para eleger a preferência do paciente na avaliação da primeira linha de tratamento do câncer de mama metastático her2 hiperexpresso

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Abstract

Background: The many combinations of chemotherapeutic agents and biologicals available in the Brazilian National Health System for the treatment of metastatic breast cancer require analysis that contribute to decision making. **Objective:** The study's primary aim was to evaluate the first-line treatment of HER2- overexpressing metastatic breast cancer from the Brazilian Unified Health System perspective using multicriteria decision analysis (MCDA). **Method:** The treatment options evaluated were (a) pertuzumab combined with trastuzumab and docetaxel, and (b) trastuzumab in combination with docetaxel. Using the hierarchical analytical method, medical oncologists compared the relevance of five predefined criteria: overall survival, response to treatment, adverse events, cost- effectiveness, and budget impact. **Results:** The therapeutic scheme considered more appropriate by the model was pertuzumab combined with trastuzumab and docetaxel. The most sensitive criteria were adverse events, cost-effectiveness, and budget impact. The results suggest that the classification has a close relationship with the perspective of healthcare professionals participating in the questionnaire. **Conclusion:** Defining the treatment of an incurable disease associated with a short survival time and high-cost treatment options necessitates complex decision-making. MCDA allows the weighting of criteria and considering criteria that would be difficult to measure in other methods, such as cost-effectiveness. These aspects differ from economic models and contribute to a broader evaluation of health decision-making.

Keywords: decision-making; analytic hierarchy process; pertuzumab; breast cancer; patients preference.

Resumo

Introdução: As diversas combinações de agentes quimioterápicos e biológicos disponíveis no Sistema Único de Saúde brasileiro para o tratamento do câncer de mama metastático requerem análises que

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contribuam para a tomada de decisões. **Objetivo:** O objetivo principal deste estudo foi avaliar o tratamento de primeira linha para câncer de mama metastático HER2 hiperexpresso sob a perspectiva do Sistema Único de Saúde, utilizando a análise de decisão multicritérios (MCDA). **Método:** As opções de tratamento avaliadas foram: (a) pertuzumabe em combinação com trastuzumabe e docetaxel, e (b) trastuzumabe em combinação com docetaxel. Usando o método analítico hierárquico, médicos oncologistas compararam a relevância dos cinco critérios predefinidos: sobrevida global, resposta ao tratamento, eventos adversos, custo-efetividade e impacto orçamentário. **Resultados:** O esquema terapêutico considerado mais apropriado pelo modelo foi pertuzumabe em combinação com trastuzumabe e docetaxel. Os critérios mais sensíveis foram eventos adversos, custo-efetividade e impacto orçamentário. Os resultados sugerem que a classificação está associada à perspectiva do profissional de saúde participante do questionário. **Conclusão:** Definir o tratamento de uma doença incurável associada a um tempo de sobrevida curto e opções de tratamento de alto custo requer uma tomada de decisão complexa. O MCDA permite ponderar e considerar critérios que seriam difíceis de medir em outros modelos de decisão. Esses aspectos contribuem para uma avaliação mais ampla da tomada de decisões em saúde.

Palavras-chave: análise de decisão multicritério; processo analítico hierárquico; pertuzumabe; câncer de mama.

INTRODUCTION

Approximately 20% of breast cancer cases present amplification or overexpression of the HER2 oncogene[1]. According to the Diagnostic and Therapeutic Guidelines for Breast Carcinoma in the treatment of HER2-overexpressing metastatic breast cancer[2,3], the proposed chemotherapy regimens seek to attenuate symptoms, improve quality of life, and increase survival[4,5].

The National Commission for the Incorporation of Technologies in Brazilian Unified Health System (CONITEC) incorporated trastuzumab in 2012 for early or advanced breast cancer provided HER2-overexpression was confirmed[6,7]. The administration of trastuzumab is adjusted to chemotherapy regimens and is used as a first-line treatment combined with taxanes (polychemotherapy) or as monotherapy in the retreatment of patients who failed multidrug chemotherapy[2].

The Brazil National Health Surveillance Agency (ANVISA) approved pertuzumab in 2013 and incorporated by CONITEC in 2017, combined with trastuzumab and docetaxel chemotherapy in the treatment of HER2-overexpressing locally advanced or metastatic breast cancer, as reported by a phase III trial [6,8-10]. The numerous combinations of chemotherapeutic agents and biological agents available from the Brazilian Unified Health System to treat metastatic breast cancer require analysis of the studies that contribute to decision-making[11].

For metastatic cancer patients, ethical issues become even more problematic. Several technologies impact a survival increase of a few months and present a cost above the acceptability threshold. Despite the high cost, one cannot disregard the relevance of this outcome in a patient's life, and the criteria valuation allowed by MCDA techniques can contribute to this decision[12]. The multicriteria decision analysis (MCDA) consider multidimensional criteria instead of seeking alternatives that best suit one or two (such as effectiveness and cost), and its use for the evaluation of health technologies has been previously discussed[13].

This study used the analytic hierarchy process method (AHP) to compare the following therapeutic regimens for first-line treatment for HER2-overexpressing metastatic breast cancer: a) pertuzumab + trastuzumab + docetaxel (PTD), b) trastuzumab + docetaxel (TD).

METHODS

Research problem characterization

The current literature has clarified several essential aspects of the disease, such as the sweeping panorama of metastatic breast cancer in Brazil and worldwide, patient access to currently available technologies, and previous studies of MCDA in the Health Technology Assessment (HTA) area[8,11,14-23]. The following electronic databases were examined in this study: MEDLINE (via PubMed), EMBASE (via Evidence-Based Health Portal), LILACS (via BIREME), Web

of Science, ScienceDirect, and records of the Cochrane Collaboration. ISPOR Task Force[13] guide the elaboration of this study.

Criteria definition

The authors' group, formed by HTA research and an oncologist, selected the model's criteria. The performed criteria selection used outcomes measured in clinical trials that evaluated chemotherapy to treat of metastatic breast cancer[8,24] and economic relevance according to economic evaluations of health technologies. The definitions of the criteria are listed below.

- Overall survival (OS): Total time between the beginning of treatment and the death of the patient;
- Response to treatment (RE): The capacity of the treatment to enable regression of measurable lesions[25];
- Adverse events (AE): Unfavorable events occurring during or after the use of medication or other intervention[26]. This criterion also refers to the capacity of the therapeutic scheme to avoid adverse events. Chemotherapy treatments may present high toxicity, which can strongly affect patient quality of life;
- Incremental cost-effectiveness ratio (ICER): The ratio of incremental cost and consequences measure in $/outcome. A more cost-effective therapeutic scheme provides more benefits to health system[27]. This criterion was selected because it is currently an indispensable factor in the evaluation of health technologies for incorporation purposes;
- Budget impact (BI): Evaluation of financial consequences of adopting a new health technology within a given health scenario containing finite resources. This type of study's central role is the forecast of the global financial impact of the adoption of a specific technology[28].

Decision problem structure

The model included three hierarchy levels, according to the AHP model structure[29]. The first level is for the primary purpose: "Treatment of patients with metastatic HER2-expressing breast cancer". The second level is for the criteria selected to reflect the opinion of the decision-maker, and the last level is for the alternatives to analyze.

The final representation of the decision hierarchy characteristics of the AHP method applied to this decision process is presented in Figure 1.

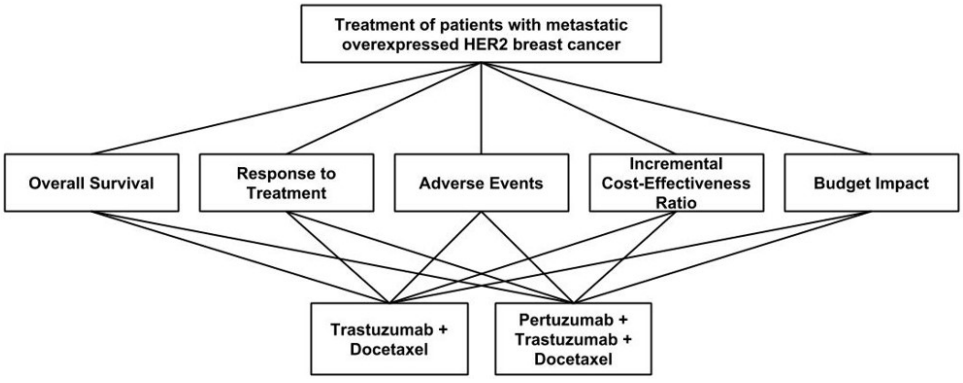

Figure 1. Hierarchical structure for the proposed problem

Web-based survey construction to criteria and alternatives evaluation

The questionnaire included questions necessary to evaluate the performance of the technologies and the weight of the criteria listed. The survey used the online interface of

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SurveyMonkey[30], and the purpose was to collect data of the clinical practice from medical oncologists. The participants answered questions about criteria valuation and assessed the performance of the alternatives but did not participate in the criteria selection process. Also, the questionnaire included an open question allowing the participants evaluate criteria on their choice, but we had no answers for that. The Research Ethics Committee (CEP) of the Institute of Social Medicine accepted the study, under registration CAE 59076316300005260. This research was performed in compliance with ethical principles, according to the Helsinki Declaration[31] and the Brazilian legislation issued by the Research Ethics National Committee[32].

Data processing

The data was processed using MS Excel® software. Each item of the questionnaire was grouped using the geometric mean of the responses. These data served as input parameters for the AHP model. The next step was the construction of the model, which comprised the following actions: a) data normalization and b) data grouping through the sum of products between the performance of a technology in a criterion and the weight of the criterion. We then calculated the global priority vector of each alternative.

The consistency of the model was calculated by the following Equation 1:

$$\det\left[A - \lambda I\right] = 0 \quad (1)$$

where: A = matrix developed by the AHP method, λ = eigenvalue, I = identity matrix.

The largest eigenvalue of the matrix represents the most significant root of the resulting matrix equation[29].

To verify the robustness and stability of the model, a sensitivity analysis was conducted by varying the weight of the criteria and evaluating the impact of this mechanism on the AHP model.

RESULTS

Answers obtained by the questionnaire

The questionnaire generated 60 accesses and 27 answers with sufficient information to the model. The next sections present the data generated by the responses related to the AHP model.

Relative weight among criteria

The relative weights of the criteria were determined by normalizing the data obtained through the questionnaire (Figure 2).

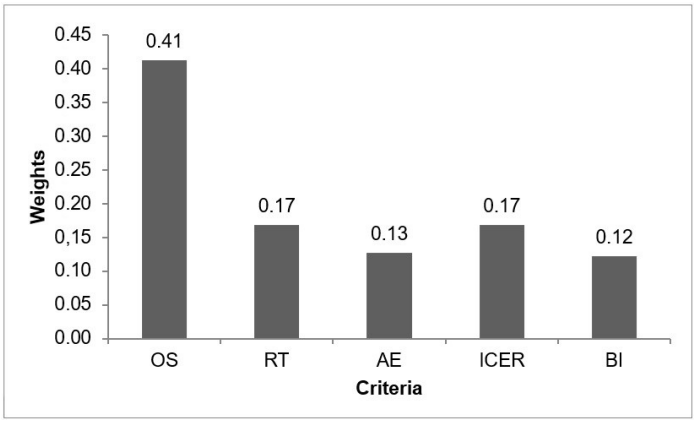

Figure 2. The relative study criteria weights

The aggregation of answers revealed OS criterion obtained the highest order of preference at 41%. The lowest criteria were budget impact and adverse events with approximated values of 12% and 13%, respectively.

Alternatives evaluation

The criteria presented previously and their relative weights were used to evaluate the two treatment alternatives for HER2-overexpressing metastatic breast cancer. Figure 3 contains the importance indices of the alternatives per criterion based on the relative importance between criteria and the comparison of each alternative for each criterion.

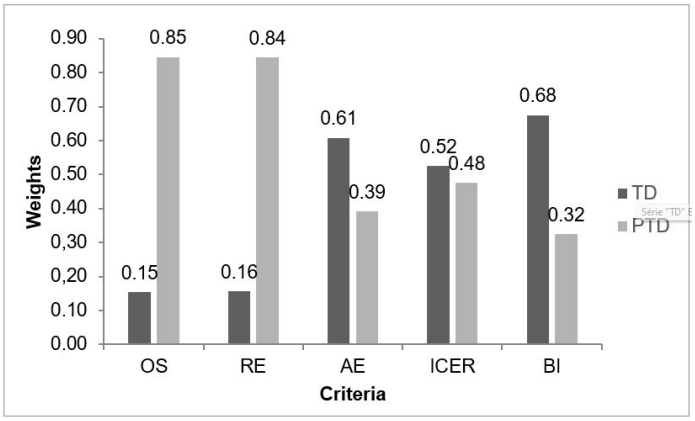

Figure 3. Comparison of performances by criterion

Global score of alternatives

Global score is the relative importance between each of the alternatives and was considered the highest value as the solution (or the best solution) to the problem. The results shown in Figures 3 and 4 indicate that the PTD alternative score (pertuzumab combined with trastuzumab and docetaxel) obtained superior performance. The difference between the two therapeutic regimens evaluated was approximately 0.3 and was mostly due to the high importance of OS and response criteria. The PTD alternative demonstrated better performance for both criteria.

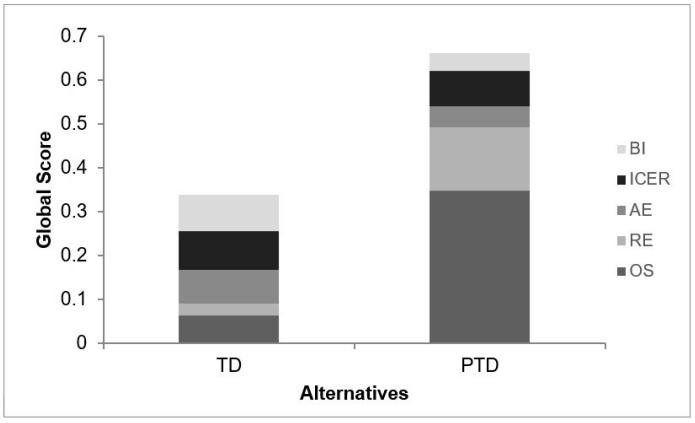

Figure 4. Global score of alternatives

Consistency test

The upper limit agreed by Saaty for the consistency ratio is 10%, or 0.1[20]. The consistency ratio for the performance matrices of the alternatives was 0 due to the existence of only two

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alternatives. There was a consistency ratio of 0.01 for the matrix of comparisons between criteria within allowable limits determined by the author.

Sensitivity analysis

We conducted a sensitivity analysis in five stages. In each stage, we varied the relative importance (weight) of one criterion and distributed the difference between the original value and the modified amount proportionally based on the weight of the other criteria. To analyze the effect of the weight variation in its entire range (0 to 1), we established 0.1 as the variation rate.

The sensitivity analysis results suggest that even with criteria weights varying from 0 to 1 (lower and upper limits) the pertuzumab-based treatment alternative combined with trastuzumab and docetaxel was superior in overall survival and response to treatment criteria.

The criteria that presented sensitivity were the following: adverse events, cost-effectiveness, and budget impact. For the budget impact criterion, an increment of 40% to 45% could change the model's result and showed the highest overall score for the TD alternative. The adverse events criterion showed similar behavior so that an increase of approximately 45% to 50% of its weight could alter the final decision and favor the TD therapeutic scheme. This TD option would also be possible if there was an increase of approximately 70% in the weight of the cost-effectiveness criterion.

DISCUSSION

The result of the model indicates that pertuzumab in combination with trastuzumab and docetaxel, would be the best option for first-line treatment of HER2-overexpressing metastatic breast cancer patients. However, access to this drug must be appropriately given. Studies report difficulties experienced by users of the Brazilian Unified Health System with breast cancer if accessing chemotherapy treatments already incorporated in the public network[20-23,33].

Previous studies published on this subject have shown unfavorable cost-effectiveness of pertuzumab combined with trastuzumab and docetaxel for the same indication evaluated[34-36]. The conclusions of these studies corroborate the evaluation of the respondents to the questionnaire for the cost-effectiveness criterion. The incremental cost-effectiveness ratio is one of the primary decision-making tools for the incorporation of health technologies. Thus, unfavorable results for this outcome are a significant concern regarding the use of therapy and the need for rational use of resources in the health sector. International agencies such as CADTH and NICE favor the therapeutic scheme's inclusion if the drug's cost is within acceptable limits[37,38].

It is worth discussing the use of MCDA/AHP methods in the context of evaluating health technologies. All methods have their limitations. The choice of one or the other depends on many objectives and goals intended to be achieved[39]. The choice of the method depends on the objectives of the study. Although more sophisticated methods of MCDA have developed, they do not always bring more meaningful answers[40] and are often a cause of distrust for managers who have difficulty understanding and accepting their conclusions and incorporating technology[41]. According to Dolan (2005)[42,] " The AHP has a number of advantages over other multicriteria techniques including a firm theoretic basis, flexibility, relative ease of use, and a built- in check on the consistency of the judgments made during the course of an analysis. These advantages have led to widespread use of the AHP in many practical applications."

Different from economic evaluations, AHP methods allow criteria that are difficult to measure objectively. Also, through AHP, it is possible to determine weights for the criteria, causing considerable variation in the results. Another advantage of using AHP in HTA is the possibility of allowing the participation of patients, regulatory agencies, and managers, in addition to the professionals that provide care[43]. Nevertheless, this method's use in HTA still lacks standard protocols and guidelines for execution and the mechanisms that deal with uncertainties associated with the subjectivity that permeates this method's input parameters.

As for this method's practical application, the system proved suitable for the intended purpose. Once the model is completed, it is possible to improve it as new decisions are made continually.

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The limitation of this research was the difficulty in gathering many experts on the subject specified to act as decision-makers during the model's development. This limitation could be addressed in future studies by using face-to-face meetings with experts, even though using a survey aimed at collecting more responses. Although this approach could limit the number of participants, it would ensure data collection.

Progression-free survival (PFS) is the time between initiation of therapy and the onset of tumor progression. Over the last decade, new drugs have received regulatory approval for metastatic breast cancer by only demonstrating improved progression-free survival without a concomitant increase in overall survival (OS). The advantages of using PFS will be time savings and lower drug development costs, which ultimately improves patient access to new drugs[44]. However, the clinical relevance of PFS is unclear and may often be an inadequate surrogate of OS[45].

Since the present study draws on expert opinion, the advantages of using PFS were pondered less relevant than OS. Although the combination of pertuzumab, trastuzumab, and docetaxel was better evaluated in the OS and Response to Treatment criteria, this therapeutic regimen also presented the worst performance in the Adverse Events. For patients with metastatic breast cancer, an incurable disease, survival is a critical outcome. However, the adverse events patients consider bearable must be evaluated relative to the incremental survival benefit the technology can provide. If other stakeholders or patients answered the questionnaire, then this model's results might lead to changes in the classification of alternatives. Also, for avoiding overlapping among the criteria, we tested the results without considering the RCEI in the analysis. In this scenario, pertuzumab would still be the preferable decision, with a score around 65%.

CONCLUSION

The data extracted from our questionnaire corroborate the results in the current literature for both effectiveness and economic outcomes[8,34-36]. Pertuzumab, trastuzumab, and docetaxel in combination, would be the best option for patients with HER2-overexpressing metastatic breast cancer. The highest value of the overall PTD alternative score is also consistent with the Ministry of Health's recent decision regarding its incorporation.

Studies such as these are useful for understanding other innovative pharmacological agents' perspectives for different stakeholders, helping to establish research priorities and evaluation. In comparison with other diseases, with more significant incremental gains, the pricing and reimbursement decision making process, for example of the treatment of rare or metastatic diseases, will remain challenging. Diseases with high average individual costs or system costs, for which there are different therapeutic strategies, can be priority targets for evaluation[46,47].

This work demonstrated the use of the AHP as a possible tool to support decision-making for treating patients with metastatic breast cancer and the understanding of evaluation criteria for this type of decision. AHP models may support decisions involving ethical issues that are difficult to compute in economic evaluations, such as metastatic breast cancer.

Future studies are also relevant to produce studies that demonstrate ways to integrate MCDA results with those obtained through economic evaluations, given their extreme importance to HTA.

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