Acta Oncologica

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ionc20

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To cite this article: Anouk K. M. Claessens, Jan J. V. Busschbach, Bram L. T. Ramaekers, Frans L. G. Erdkamp, Jeanette M. Bouma, A. Elise van Leeuwen-Stok, Vivianne C. G. Tjan-Heijnen, Monique E. M. M. Bos & on behalf of the Dutch Breast Cancer Research Group (BOOG) (2022) Cost-effectiveness of continuous versus intermittent chemotherapy for patients with HER2-negative advanced breast cancer, Acta Oncologica, 61:5, 619-624, DOI: 10.1080/0284186X.2022.2033832

To link to this article: https://doi.org/10.1080/0284186X.2022.2033832

ACTA ONCOLOGICA
2022, VOL. 61, NO. 5, 619–624
https://doi.org/10.1080/0284186X.2022.2033832

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LETTER TO THE EDITOR

Cost-effectiveness of continuous versus intermittent chemotherapy for patients with HER2-negative advanced breast cancer

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ARTICLE HISTORY Received 8 November 2021; Accepted 21 January 2022

Background

The Dutch Stop & Go study (BOOG 2010-02) compared an interrupted chemotherapy schedule with pre-defined breaks in treatment to a standard continuous schedule for patients with advanced HER2-negative breast cancer [1]. The Stop&Go study assumed a noninferiority margin of 1.34 for the upper limit of the 95% confidence interval (CI) for the hazard ratio (HR) of the primary outcome first-line progression-free survival (PFS). Such non-inferiority could not be confirmed, with a median first-line PFS of 7.4 months for intermittent, compared with 9.7 months (HR 1.17; 95%CI 0.88–1.57) for continuous scheduling [1]. Additionally, secondary analysis of the overall survival (OS) showed a benefit in favor of continuous scheduling (medians 17.1 vs. 20.9 months, HR 1.37; 95%CI 1.03–1.84) [2]. Furthermore, no clear difference in QoL was found [3]. Although we could not show that intermittent treatment was noninferior to continuous treatment in terms of (progression-free) survival outcomes, it could still be that intermittent treatment has a favorable societal impact, if the relative small reduction of the effectiveness comes with a considerable saving of costs. A Dutch study found an increase in total healthcare costs for breast cancer from €199 million in 2003 to €692 million in 2011 [4]. These costs are highest for the more advanced stages of breast cancer, [5–7] in the final year of life, [8–12] and after progression of disease, [7,10,11] underlining the importance of (cost)effective treatment management of advanced breast cancer (ABC). In order to explore this line of reasoning further, we examined the cost-effectiveness of continuous versus intermittent treatment for patients with locally advanced incurable or metastatic HER2-negative breast cancer who had not received chemotherapy for advanced disease.

Methods

This cost-effectiveness study examines whether the additional costs of continuous treatment (standard of care) are worth the additional health benefits compared to intermittent treatment, based on data collected in the Stop&Go study.

Patient selection from the Stop&Go study

Data regarding OS, QoL, and resource utilization were collected in the phase III Stop&Go study [1]. The Stop&Go study included patients ($N = 420$) with locally advanced incurable or metastatic HER2-negative breast cancer who had not received chemotherapy for advanced disease. Participants were randomized to intermittent chemotherapy (two times four cycles; second set of four cycles of the same regime in case of progression after at least 3 months) or continuous chemotherapy (one set of eight cycles), both in first- and second-line treatment. First-line chemotherapy comprised paclitaxel, which was combined with bevacizumab that was continued as maintenance treatment, also during the chemotherapy break in the intermittent group. Second-line treatment comprised either capecitabine or non-pegylated liposomal doxorubicin. Patients who fulfilled at least one QoL measurement were selected for the present economic analysis ($N = 402$, 96% of total).

Cost collection

The economic assessment was based on study-related, direct medical costs made during study-treatment. We collected medical study costs over a maximum period of 24 months

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Supplemental data for this article can be accessed here.

after randomization as we presumed on forehand that most patients would have completed study treatment within this timeframe; that is would have stopped with either the original continuous or intermittent therapy scheme, and either started follow-up treatments or did not receive further anti-tumor treatments. Costs generated after end of study-treatment and indirect costs were not included. A total of 12 patients in the continuous and 14 patients in the intermittent treatment group generated study-related costs beyond 24 months (total 6.5% of study population), which were not included in these analyses. Details on data collection and prizing can be found in the Online Supplement.

Statistical analyses

Mean life years per treatment arm were estimated by calculating the total number of Life Years (LY) between randomization and death or 24 months after randomization, whichever came first. The difference between the groups represented the LY gained.

Quality-Adjusted Life-Years (QALYs) were calculated as a measure of overall health benefit from the available QoL data as measured by the 36-Item RAND Health Survey. The RAND-36 was administered by post, at baseline and at regular intervals of 3 months [3]. Time horizon was 24 months, calculated beyond date of randomization. To estimate QALYs, we applied the syntax provided by Brazier (personal communication and Brazier et al. [13]) to convert QoL data as measured by the RAND-36 questionnaires to so called 'utility scores', rated on a scale where 0 reflects a state equal to dead and 1 to full health. For this procedure 11 of the 36 questionnaire items were used [13]. Further information on statistical methods for calculation of QALY's can be found in the Online Supplement.

Differences in several costs (medication, hospital visits, disease assessments, concurrent non-study anti-tumor treatment, and total costs) were analyzed with Mann–Whitney U-tests. Cost-effectiveness was quantified using Incremental Cost-Effectiveness Ratios (ICERs) in €per QALY and €per LY gained [14,15]. ICERs were calculated as the quotient of the difference in costs and QALYs or LYs gained. Calculated QALYs, LYs and costs were bootstrapped using sampling with replacement, using 10,000 samples. The outcomes were graphically depicted in a scatterplot to visualize the uncertainty of the estimates regarding the incremental costs and incremental benefits. In this graph, the willingness-to-pay threshold was also included. This refers to the amount a society is willing to pay to obtain 1 QALY (i.e., 1 additional year in full health) [16]. The Dutch willingness-to-pay threshold for severe diseases is established at €80,000/QALY [17]. Next, the probability that continuous therapy is cost-effective compared to intermittent therapy was graphically represented using cost-effectiveness acceptability curves (CEAC) [18].

Statistical analyses were performed with SPSS software (version 23; IBM Corp, Armonk, NY, USA). *P*-values lower than 0.05 were considered significant. R (version 4.0.1) was used for bootstrapping.

Sensitivity analyses

As previous studies found no OS benefits of adding bevacizumab to paclitaxel chemotherapy, [19,20] current international guidelines for treatment of ABC recommend to consider bevacizumab in combination with chemotherapy only in selected cases [21]. To explore uncertainty of our data, we *post hoc* subjected use of bevacizumab to sensitivity analyses. We estimated costs and ICERs in case bevacizumab would not have been used in the Stop&Go study, assuming similar outcomes.

Results

A total of 402 patients were found eligible for the current analyses (i.e., fulfilled at least one QoL measurement). A total of 2201 utility scores were calculated out of these questionnaires, with 68 missing utility scores (>2 out of the required 11 items missing).

Clinical outcomes

Baseline characteristics of the 402 eligible patients were well-balanced between randomized groups (Online Supplement Table 1).

Cost-effectiveness analysis

The estimated mean QALYs were 0.912 (SD ±0.44) and 0.891 (SD ±0.47) for continuous and intermittent treatment, respectively. Mean utility (estimated through dividing QALY by LYs) for QoL was 0.603 for the continuous and 0.614 for the intermittent group.

Average costs per patient, accumulated during the 24 months study period, were €65,740 for the continuous and €61,290 for the intermittent treatment group, leading to incremental costs of €4450 for the continuous treatment. Cost drivers (>€5000 per patient) were in descending order: treatment with bevacizumab, planned hospital visits for administration of study-treatment, treatment with non-pegylated liposomal doxorubicin, hospitalizations (overnight stays), and radiotherapy (Table 1). Consistently, the bootstrapped results indicated that continuous treatment would be more effective (survival and QALY gains of 0.061 and 0.021, respectively) and more costly (€4.454 additional costs) than intermittent treatment. This resulted in ICERs of €72,614 and €210,140 per LY and per QALY gained respectively (Table 2) for continuous versus intermittent therapy.

Figure 1 represents the individual point estimates of the ICERs of all 10,000 bootstrapped samples in an incremental cost-effectiveness plane. Most dots (65%) of the QALY-plane are plotted in the upper right quadrant, indicating that continuous treatment generates more QALYs but is also more costly than intermittent therapy. Likewise, within the LY-plane the majority (78%) of the dots are in the upper right quadrant, where continuous treatment generates more LYs but is more costly than intermittent therapy.

Table 1. Costs per patient during Stop&Go study-treatment per treatment arm (maximum up to 24 months after randomization), indexed to 2019 cost prices.

Cost-variable	Continuous treatment arm ($n = 202$)			Intermittent treatment arm ($n = 200$)			
	N=	Mean* costs	SD	*N*=	Mean* costs	SD	*p*-Value**
Medication							
Study anti-tumor treatment							
Paclitaxel	201	€ 290	€ 105	200	€ 222	€ 99	
Bevacizumab	201	€ 46,669	€ 29,597	199	€ 44,958	€ 32,708	
Capecitabine	96	€ 809	€ 400	92	€ 500	€ 263	
Non-pegylated liposomal doxorubicin	37	€ 7143	€ 3409	30	€ 5604	€ 1970	
Other medication							
Prophylactic anti-emetics	201	€ 98	€ 49	200	€ 70	€ 38	
Co-medication[a]	173	€ 2506	€ 3583	163	€ 1997	€ 3057	
Hospital visits							
Visits for administration of study-treatment	201	€ 7074	€ 2927	200	€ 6015	€ 3197	
Hospitalization (overnight stay)	74	€ 5200	€ 6200	72	€ 5442	€ 4903	
Invasive interventions during hospitalizations	31	€ 1181	€ 2500	42	€ 1022	€ 1643	
Disease assessments							
Outpatient hospital visits with oncologist	202	€ 2185	€ 1038	200	€ 1985	€ 1074	
Laboratory assessments	202	€ 860	€ 413	200	€ 790	€ 443	
Imaging	202	€ 2383	€ 921	200	€ 2291	€ 1007	
Concurrent non-study anti-tumor treatments							
Radiotherapy	20	€ 5197	€ 1777	10	€ 5630	€ 2092	
Systemic anti-tumor treatment[b]	2	€ 788	€ 1110	6	€ 996	€ 1100	
Total all costs	**202**	€ **65,740**	€ **36,540**	**200**	€ **61,290**	€ **39,709**	**0.056**

[a]Comedication consisted of the following categories: non-steroidal anti-inflammatory drugs (NSAIDs), opioids, other painkillers, anti-hypertensive agents, bisphosphonates or denosumab, other non-anti-tumor medication, given during the study-treatment period.
[b]Systemic anti-tumor treatments could consist of endocrine therapy, immunotherapy or chemotherapy other than the prescribed study medication, given during the study period (protocol violation).
*Mean costs represent conditional means for the selected population. **Calculated using Mann–Whitney *U*-tests.
SD: standard deviation.

Table 2. Cost-effectiveness results (based on bootstrap).

Treatment arm	LY	LY gained	**QoL**[a]	QALY	QALY gained	Total costs	Incremental costs	Incremental costs per LY gained	Incremental costs per QALY gained
Base case									
Continuous	1.513	0.061	0.603	0.913	0.021	€65,756	€4,454	€72,614	€210,140
Intermittent	1.451		0.614	0.891		€61,302			
Sensitivity scenario: no use of bevacizumab									
Continuous	1.513	0.061	0.603	0.913	0.021	€17,140	€2,901	€47,557	€138,143
Intermittent	1.451		0.614	0.891		€14,239			

LY, QoL and QALY are all presented in mean values. Costs are presented in 2019 Euros.
[a]QoL is calculated here as QALY/LY and represents the mean utility score for QoL while alive.
QoL: Quality of Life; QALY: quality-adjusted life-year; LY: life years.

The probability that continuous treatment is cost-effective over intermittent therapy at the national willingness-to-pay level of €80,000/QALY is 21.8%. Results are displayed in an cost-effectiveness acceptability curve (CEAC) in Online Figure 1.

Sensitivity analysis

Without the costs for bevacizumab while assuming comparable outcomes, total costs would be €17,140 for continuous and €14,239 for intermittent treatment, leading to incremental costs of €2901 and ICERs of €47,557/LY and €138,143/QALY gained respectively (Table 2).

Discussion

The present cost-effectiveness analyses of data from the Stop&Go study within the first 24 months indicates small survival as well as QALY gains with continuous chemotherapy scheduling of eight consecutive cycles compared to an interrupted schedule of two times four cycles in first- and second line treatment in patients with advanced HER2-negative breast cancer. However, these small benefits of continuous therapy do not seem to offset the additional costs: with ICERs of €72,614/LY gained and €210,140/QALY gained, the continuous chemotherapy strategy cannot be considered cost-effective compared with intermittent therapy, considering the Dutch national willingness-to-pay threshold of €80,000/QALY.

Previous studies [22], including earlier publications of the Stop & Go study [1,2], concluded to continue chemotherapy as long as possible up to 8 cycles. Within the Stop&Go study, median OS for all 420 randomized patients was respectively 20.9 versus 17.1 months for continuous versus intermittent treatment [2]. According to the Dutch national committee for assessment of oncological agents, this benefit in OS of more than 12 weeks is considered effective [23]. Additionally, several studies showed that QoL outcomes were not harmed by longer durations of (consecutive) chemotherapy treatment [3,24], Here, we report small gains in QALY's and LY gained with continuous treatment within a time horizon of 24 months that did not outweigh the small mean additional costs of €4450. It should be noted that earlier reports from the Stop&Go trial presented analyses based on data beyond

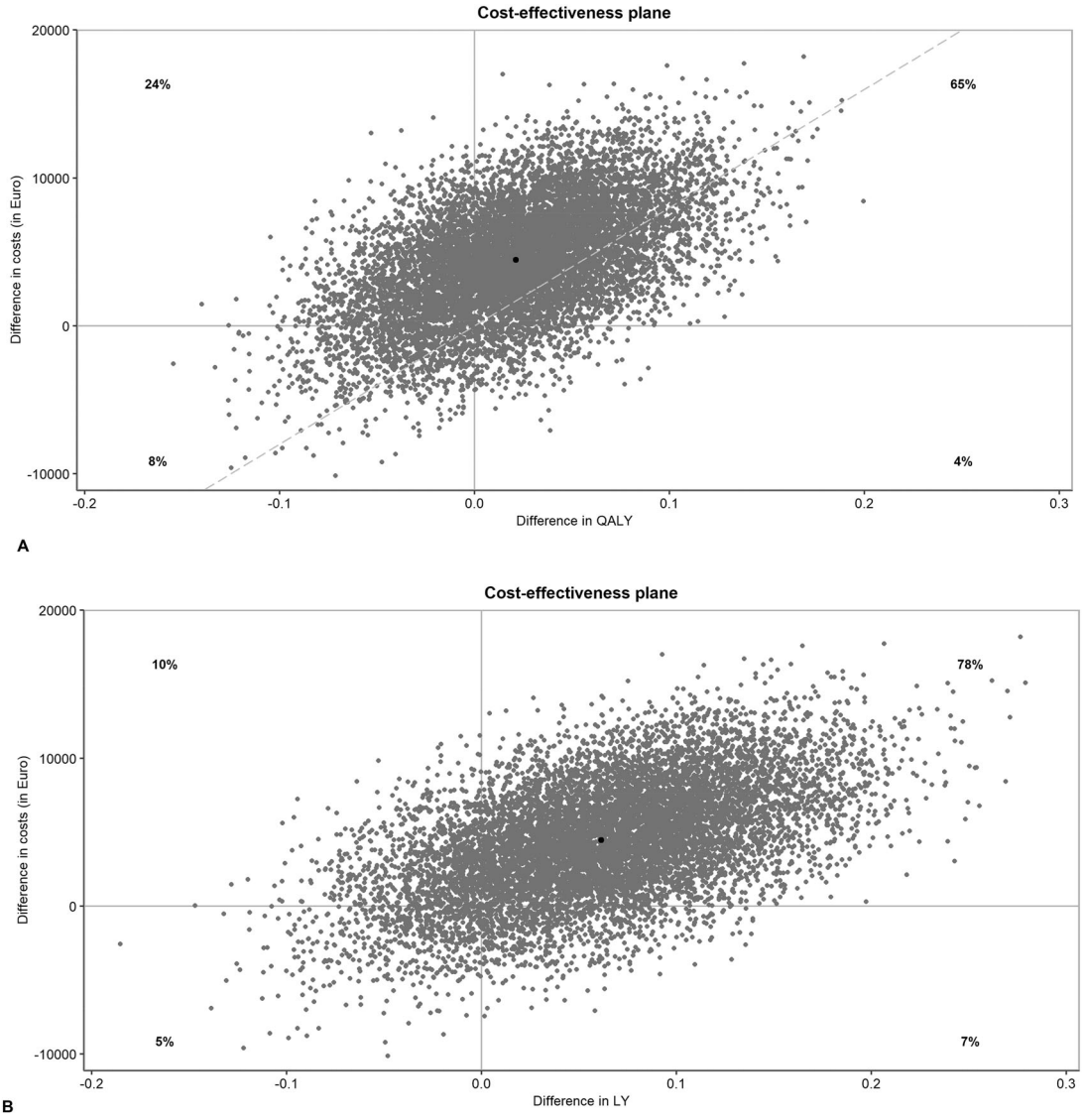

Figure 1. Cost-effectiveness planes of individual point estimates of the ICERs for QALY (A) and LY (B) gained of all 10,000 bootstrapped samples. The incremental costs and incremental benefits are demonstrated for continuous over intermittent treatment. The Y-axis expresses costs, where positive values indicate incremental costs for continuous therapy and negative values indicated incremental costs for intermittent therapy. On the X-axis QALYs (fig A) and LYs (fig B) are expressed, with positive values indicating benefits in these outcomes for continuous treatment and negative values indicating benefits for intermittent treatment respectively. ICERs: Incremental cost-effectiveness ratios; QALY: Quality-Adjusted Life-Year; LYs: life year.

24 months [1–3]. As we did not have sufficient quality costs data beyond 24 months, and because the interpretation becomes more and more difficult due to different follow up treatments, we truncated the analysis at 24 months. If the studied time horizon would be extended, the survival gains of continuous treatment would potentially increase, increasing the estimated QALYs and likely improving its cost-effectiveness. Furthermore, the fact that differences in QALY's and LY gained found here were small, indicates that based on previously published (clinical) outcomes the continuous chemotherapy strategy should be preferred.

The major cost-driver in our analysis was the use of bevacizumab (Table 2) while in current clinical practice bevacizumab is only recommended by international guidelines to be considered in combination with chemotherapy in selected cases [21]. Additionally, the use of bevacizumab in combination with first-line chemotherapy was already reduced after the FDA provoked their approval in 2011 [25] and will probably further decline due to the recent introduction of new treatment options for ABC. We performed *post hoc* sensitivity analyses leaving out the costs of bevacizumab treatment. These analyses generated ICERs of €47,557/LY and €138,143/QALY for continuous over intermittent treatment, a ratio closer to the national willingness-to-pay threshold of €80,000/QALY. Noteworthy, bevacizumab will be out of patent in the near future which may thus impact our ICER results [26].

Despite large discrepancies in methods used, other studies in ABC patients receiving comparable therapy report similar health-state utility scores. Specifically, a Dutch cost-effectiveness study on the use of bevacizumab in HER2-metastatic breast cancer, partly using the same treatment agents and within the same country as our study, reported cross-sectional EQ-5D health-state utilities in the real-world population of 0.66 and 0.55 for the progression-free and progressive disease health states respectively [27].

Dedes et al. used utility scores of 0.61 for stable disease and 0.26 for progressive disease in their Markov model-based cohort simulation for ABC patients treated with bevacizumab and paclitaxel [28].

Conclusion

Our results suggest that in advanced HER2-negative breast cancer patients, continuous chemotherapy in first- and second-line, cannot be considered cost-effective compared to intermittent chemotherapy. However, results were largely influenced by the costs of bevacizumab when taking the sensitivity results into account. Therefore, we recommend to guide chemotherapy duration primarily on clinical effectiveness and quality of life rather than on cost aspects.

Acknowledgements

We thank all patients, physicians (research)nurses and local data managers who participated in the Stop&Go trial; the members of the steering committee, the data safety monitoring committee, the central data management from the Comprehensive Cancer Centre the Netherlands, especially Steffen de Groot; and the Dutch Breast Cancer Research Group. We thank the teams from F. Hoffmann-La Roche Ltd and TEVA Nederland B.V. for their support.

Disclosure statement

FE has received honoraria from Roche and Novartis and has a consulting/advisory role for these companies. EvL has received research funding for her institution from Roche and TEVA. VTH has received honoraria and/or travel, accommodations and/or expenses from Pfizer, E. Lilly, Novartis and Roche, has a consulting or advisory role for Pfizer, E. Lilly, Novartis and Roche, has received research funding for her institution from Roche, Eisai, Pfizer, E. Lilly, Novartis, and AstraZeneca. MB has received Travel, accommodations and/or expenses from Roche, Novartis and Pfizer. All remaining authors have declared no conflicts of interest.

Funding

This study was funded by F. Hoffmann-La Roche Ltd, the Netherlands and TEVA Nederland B.V. These companies had no input in the design and/or analysis of this cost-effectiveness study.

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Data availability statement

Additional data on the trial protocol can be found at the EU Clinical Trials Register, using number 2010-021519-18 (https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-021519-18). The datasets generated and analyzed during the current study are not publicly available due to confidential cost-prices. Data are however are available from the corresponding author on reasonable request.

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