First-line Bevacizumab plus Taxane-based Chemotherapy for Metastatic Breast Cancer: Cost-minimisation Analysis

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Abstract. *Aim: To carry out a cost minimisation analysis including a comparison of the costs arising from first-line treatment by bevacizumab plus docetaxel (BD) versus bevacizumab plus paclitaxel (BP) of patients with metastatic breast cancer (mBC). Patient and Methods: All consecutive patients with human epidermal growth receptor 2-negative mBC and treated at Besançon University hospital between 2006 and 2010 by a first-line therapy containing bevacizumab plus taxane were retrospectively studied. Economic analysis took into account costs related to drugs, hospitalization and healthcare travel. Results: Progression-free survival difference between the two treatments was insignificant (p-value=0.31). BP treatment was associated with a higher mean total cost than that of BD treatment, €53,093±34,395 versus €60,196±48,766, respectively. Conclusion: Whereas bevacizumab is recommended for first-line treatment of mBC with paclitaxel-based chemotherapy, our study has shown that BD treatment is the most cost-efficient regimen. It could be an attractive option in France, with a potential cost saving of €24,000,000 per year.*

The economic burden of metastatic breast cancer (mBC) is considerable (1-6). New therapeutic options have dramatically increased the cost of treatments, especially of targeted therapies, such as bevacizumab (6-9).

Bevacizumab is a humanized monoclonal antibody directed against all isoforms of vascular endothelial growth factor-1, and has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for routine use in combination with paclitaxel since 2008, and with docetaxel since 2009, for patients who have not undergone chemotherapy for metastatic human epidermal growth receptor 2-negative (HER2) breast cancer. Combination of bevacizumab with paclitaxel or docetaxel significantly improves efficacy of first-line therapy *versus* the agents alone, with a median progression-free survival of 11.8 months (hazard ratio=0.60, *p*-value <0.01) and 10.1 months (hazard ratio=0.77, *p*-value=0.06) respectively, without significant improvement in overall survival (10-11). The combination of bevacizumab with chemotherapy was associated with a limited increase in the toxicity of chemotherapy. Another randomized phase III study, RIBBON-I, demonstrated a significant improvement in terms of progression-free survival when bevacizumab was combined with taxane- and anthracycline-based chemotherapy or capecitabine monotherapy (12). Smith *et al* conducted an open-label study including 2,251 patients to assess first-line bevacizumab with taxane-based chemotherapy in routine oncological practice (13). The safety and efficacy of bevacizumab-taxane therapy were consistent with results of randomized first-line trials. Thus, bevacizumab plus taxane was considered as a standard of care for first-line metastatic breast cancer (14). However, to date, no study has directly compared bevacizumab plus docetaxel with bevacizumab plus paclitaxel.

In December 2010, following a review of the relevant data, the FDA and the Agency's Committee for Medicinal Products for Human Use recommended that bevacizumab should only be given in combination with paclitaxel for the treatment of mBC, and the concomitant registration for its use with docetaxel was canceled (15, 16).

In the context of rational decision-making in health care, a major challenge in pharmacoeconomic evaluation is to provide cost-effectiveness data that are relevant to daily practice and that may be required to optimize consumption of healthcare resources. Thus, the purpose of this study was to carry out a cost-minimisation analysis including a comparison of the costs to the French Public Healthcare System perspective, arising from first-line treatment by

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bevacizumab plus docetaxel *versus* bevacizumab plus paclitaxel for patients with mBC.

Patients and Methods

Patients. All consecutive patients treated at Besançon University Hospital, between July 2006 and March 2010, by a first-line therapy containing bevacizumab plus taxane were retrospectively studied. All patients had histologically confirmed metastatic HER2-negative breast cancer. No patient had undergone prior cytotoxic therapy for metastatic disease. Previous hormonal therapies for mBC, cytotoxic adjuvant chemotherapy and adjuvant hormonotherapy were allowed.

First-line treatment. All patients included were treated with an intention to treat (ITT) basis by either bevacizumab at 15 mg/kg plus docetaxel at 100 mg/m^2 every 3 weeks; or bevacizumab at 10 mg/kg on days 1 and 15 plus paclitaxel at 80 or 90 mg/m^2 on days 1, 8 and 15 of each 4-week cycle. Bevacizumab was given until disease progression, unacceptable toxicity or clinical judgment to discontinue, and was routinely administered as maintenance treatment after the completion of chemotherapy.

Cost-minimisation analysis. This retrospective economic study was a cost-minimisation analysis, with patients treated with ITT. An initial postulate was required *i.e.* that the clinical effectiveness did not statistically differ between the two regimens.

The cost-minimisation analysis was performed from the French Public Healthcare System perspective. Only direct medical costs were included in our analysis. They were collected from the first to the last cycle of first-line therapy. Minor costs and costs considered to be independent of the treatment arm were not taken into account (such as premedications); nor were indirect medical and intangible costs. Costs are expressed in Euros (€).

Major resources used were identified for each patient: drugs (bevacizumab, paclitaxel, docetaxel), hospitalization for drug administration (outpatient visits), hospitalization for serious adverse events management, and healthcare travel. It is important to note that in France, the trip to the site of treatment (*i.e.* home to hospital) is charged to the healthcare system. All of these parameters were collected from available computerized data and patient medical records for each individual case.

For drugs administered in the hospital (bevacizumab, docetaxel, paclitaxel), we determined the exact number of milligrams per prescription and per patient, and then multiplied this quantity by the purchase price of each drug. Unit prices of drugs were obtained from wholesale price lists from our hospital (year 2011 values).

Hospital resource costs were based on the French public Diagnosis-related Group (DRG) database, which is used to fund each hospital stay, and does not include expensive drugs such as bevacizumab (http://atih.sante.fr). All resources were therefore included for each hospital except these expensive drugs.

Healthcare travel costs were estimated for each patient using the number of cycles of chemotherapy and the total hospital admissions. Patient travelling costs were based on one return trip by ambulance per hospital admission, using the distance from home to hospital, according to the French Public Healthcare System (year 2011 values, http://ameli.fr).

As our study took place over a limited period of time, no discounting was performed. Unit prices or costs are summarized in Table I.

Table I. *Unit costs and prices (year 2011 value).*

	Unit cost (€)
DRG database	
Chemotherapy administration (day ward, outpatient)	400.68
Drugs (per milligram)	
Bevacizumab	3.2696225
Docetaxel	0.0658545
Paclitaxel	0.0816800

Clinical assessment. Our economic analysis was based on the assumption that the effectiveness of the regimen of bevacizumab plus docetaxel and that of bevacizumab plus paclitaxel was similar. Thus, progression-free survival was compared between these two regimens.

Statistical analysis. The primary end-point was progression-free survival, defined as the time from the start of chemotherapy to disease progression or death by any cause. Progression-free survival was analyzed using the Kaplan-Meier method for each treatment arm. The difference between the two treatment arms was compared with the use of the log-rank test, with the hazard ratio and its 95% confidence interval calculated from a Cox regression model with a single covariate.

Continuous variables were described by the mean±standard deviation (SD) and median with range, and qualitative variables by the size and percentage rate. Between the two cohorts, qualitative and quantitative variables were respectively compared by the Fisher exact test or the chi-square test and nonparametric Mann–Whitney test. All tests were two-tailed and significant at an alpha threshold of 5% (p-value).

Statistical analysis was performed with SAS® software version 9.1 (Cary, NC, USA).

Sensitivity analysis. To gain insight into the uncertainty concerning the cost difference, standard non-parametric bootstrap stimulations were conducted (10,000 replications).

Results

Patient population. Between July 2006 and March 2010, 83 patients were treated by first-line bevacizumab plus taxane-based chemotherapy for mBC, including 35 patients with bevacizumab plus docetaxel and 48 with bevacizumab plus paclitaxel. Demographic and baseline disease characteristics of this ITT population were generally well-balanced between the treatment arms (Table II).

Clinical assessment. Progression-free survival was similar between the two treatment regimens, with median values of 10 and 9 months for bevacizumab plus docetaxel, and bevacizumab plus paclitaxel, respectively (hazard ratio=1.28; 95% confidence interval, CI=0.80-2.04, p-value=0.31) (Figure 1).

Table II. *Demographic and disease characteristics of patients with metastatic breast cancer.*

Characteristic	Bevacizumab plus docetaxel	Bevacizumab plus paclitaxel	*p*-value
Number of patients	35	48	–
Median age (range), years	57 (29-75)	60 (41-90)	0.04
<65	27 (77)	27 (56)	0.06
≥65	8 (23)	21 (44)	
HER2-negative status, n (%)	35 (100)	48 (100)	1.00
Positive estrogen receptor status, n (%)	29 (83)	42 (88)	0.75
Positive progesterone receptor status, n (%)	20 (57)	33 (69)	0.36
Prior hormone therapy, n (%)			
(Neo)adjuvant	13 (37)	23 (49)	0.37
Metastatic	8 (23)	22 (45)	0.04
Previous adjuvant chemotherapy, n (%)			
None	22 (63)	21 (44)	0.12
Anthracycline	13 (37)	26 (55)	0.12
Taxane	4 (11)	13 (28)	0.10
Metastatic at diagnosis, n (%)	15 (43)	15 (31)	0.36
DFI between initial and metastatic diagnoses, n (%)			
>12 months	19 (54)	31 (65)	0.37
>24 months	17 (49)	26 (54)	0.66
≥3 Metastatic sites, n (%)	9 (26)	9 (19)	0.59
Site of disease, n (%)			
Liver	12 (34)	17 (35)	0.92
Lung	12 (34)	13 (27)	0.63
Bone	21 (60)	36 (75)	0.16
Bone only	6 (17)	12 (25)	0.43

DFI=Disease Free Interval; HER2=human epidermal growth receptor 2; n=number.

Table III. *Characteristics of patients during first-line bevacizumab plus taxane-based treatment for metastatic breast cancer.*

Characteristics	Bevacizumab plus docetaxel	Bevacizumab plus paclitaxel	*p*-value
Number of patients	35	48	/
Hospitalization for drug administration, mean no.±SD, median (range)			
Total	16±9 13 (5-39)	24±13 21 (6-76)	0.003
Bevacizumab plus taxane	9±5 6 (3-22)	16±5 17 (5-24)	<0.0001
Maintenance bevacizumab at 15 mg/kg every 3 weeks	8±10 4 (0-33)	8±11 4 (0-52)	0.91
Length of treatment, mean no. of months±SD, median (range)			
Total	10±7 7 (2-29)	10±7 7 (2-32)	0.99
Bevacizumab plus taxane	4±1 4 (2-7)	5±2 5 (2-8)	0.03
Maintenance bevacizumab	5±7 2 (0-25)	5±7 2 (0-24)	0.99
Hospitalization for serious adverse events management, n (%)	5 (14)	2 (4)	0.13
Length of stay, median no. of days (range)	8 (3-17)	5 (5-6)	0.37
Dose modification, n (%)			
Bevacizumab	0 (0)	0 (0)	1.00
Taxane	24 (69)	10 (21)	<0.0001
Switch from one taxane to another, n (%)	9 (26)	1 (2)	0.002
Death, n (%)	1 (3)	2 (4)	0.75

n=number; no.=number; SD=standard deviation.

Cost-minimisation analysis. Characteristics of first-line treatment in the 83 patients with metastatic HER2-negative breast cancer are summarized in Table III. Nine patients switched from bevacizumab plus docetaxel to bevacizumab plus paclitaxel due to taxane-related toxicities, compared to switching of one patient from bevacizumab plus paclitaxel to bevacizumab plus docetaxel. The number of hospitalizations for drug administrations was significantly higher for patients treated by bevacizumab plus paclitaxel compared to patients treated by bevacizumab plus docetaxel (*p*-value=0.003). Nevertheless, the total length of first-line treatment did not differ significantly between the two treatment arms, with median values of 10 (2–32) months (*p*-value=0.99).

First-line bevacizumab plus paclitaxel chemotherapy for mBC was found to have a higher mean total cost than that of first-line bevacizumab plus docetaxel chemotherapy, at €60,196±48,766 *versus* €53,093±34,395, *i.e.* a cost differential of €7,103 (Table IV). The sensitivity analysis confirms the robustness of these results, with a mean cost differential of €7,152 ($p<0.0001$). Interestingly, the drug costs represent 84% and 81% of the total cost, respectively.

Discussion

A pharmacoeconomic approach is commonly used to evaluate the health benefit of new treatments, the aim of which is to obtain good value for money. An additional approach is to optimize the economic profile of daily practices, especially in medical oncology (17-20). Economic evaluation of mBC is valuable, since it suggests efficient use of healthcare resources and provides important information to physicians and the public healthcare system. In particular, some studies suggest that bevacizumab plus taxane is not cost-effective in first-line treatment of patients with mBC (21, 22).

As of December 2010, at our University Hospital, which is the regional referent cancer center for the Franche-Comté

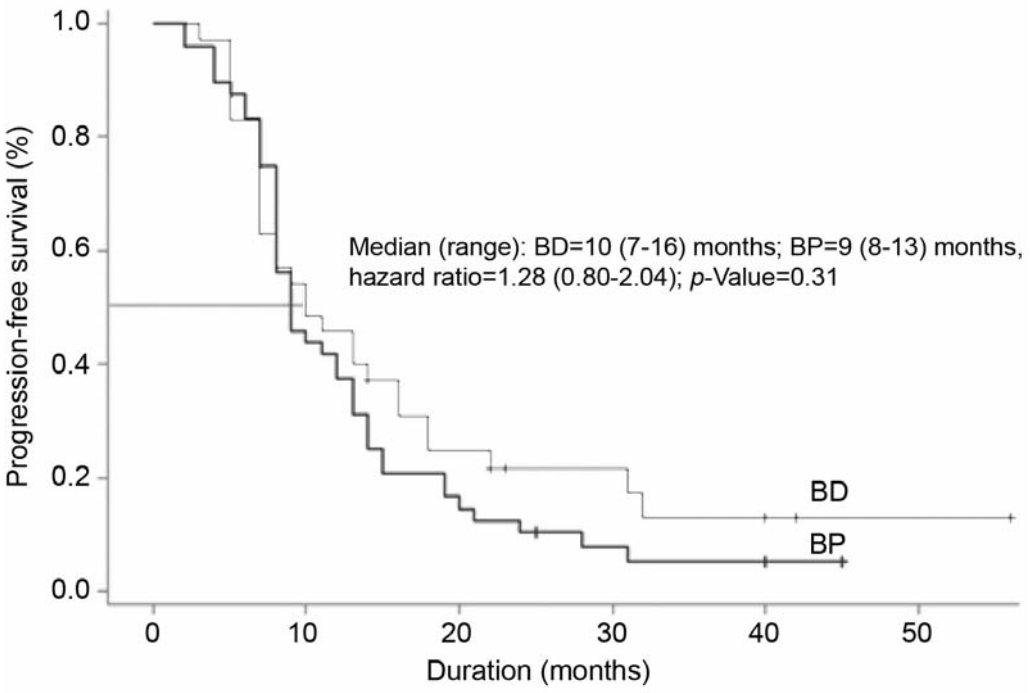

Figure 1. *Kaplan-Meier estimates of progression-free survival in patients treated by bevacizumab plus docetaxel (BD) and bevacizumab plus paclitaxel (BP) regimens.*

Table IV. *Cost minimisation analysis.*

Costs (€) Mean±standard deviation Median (range)	Bevacizumab plus docetaxel regimen (n=35)	Bevacizumab plus paclitaxel regimen (n=48)	*p*-value
Drugs	44,848±31,188 36,002 (11,025-134,498)	48,914±44,258 34,488 (8,337-288,141)	0.81
Hospitalization for			
Chemotherapy administration	6,605±3,748 5,209 (2,003-15,627)	9,533±5,263 8,414 (2,404-30,452)	0.003
Serious adverse events management	718±1,914 0 (0-7,827)	275±1,357 0 (0-7,827)	0.12
Healthcare travel	922±700 777 (107-3,303)	1,473±1,123 1,156 (237-5,290)	0.02
Total cost	53,093±34,395 45,429 (13,664-148,629)	60,196±48,766 42,811 (11,829-312,009)	
Difference of		**€7,103**	
Sensitivity analysis	53,136±5,803 52,934 (34,141-74,666)	60,288±7,030 59,744 (41,482-97,839)	<0.0001
Difference of		**€7,152**	

region, the standard first-line chemotherapy for HER2-negative mBC was bevacizumab plus taxane-based chemotherapy. The choice of taxanes, when both were allowed, depended mainly on age, hepatic function and performance status. Thus, the bevacizumab plus docetaxel regimen was proposed for younger patients with a normal hepatic function and better performance status.

However in January 2011, the standard first-line chemotherapy was modified and now only bevacizumab plus paclitaxel regimen is authorized. The conclusions of The

Agency's Committee for Medicinal Products for Human Use are as follows: "due to the negative balance of benefits and risks observed with bevacizumab plus docetaxel, it must no longer be used routinely in the treatment of metastatic HER2-negative breast cancer" (16).

Questioning the use of bevacizumab in combination with taxane has led us to assess the effectiveness, but not the efficacy, of these two regimens in pragmatic utilization, outside of clinical trials with patient selection. Interestingly, the relationship between effectiveness and costs arising from first-line chemotherapy by bevacizumab plus taxane-based chemotherapy was evaluated from the perspective of the French Public Healthcare System.

Initially, our pragmatic study assessed the effectiveness of these two regimens for all patients with HER2-negative mBC treated in our University Hospital. Demographic and baseline disease characteristics were well-balanced between treatment arms, despite the pressure for selecting paclitaxel or docetaxel based on patient profiles. Statistically, the progression-free survival was not significantly different between the two treatment arms, with median values of 10 months for patients treated by bevacizumab plus docetaxel as opposed to 9 months for patients treated by bevacizumab plus paclitaxel (hazard ratio=1.28, *p*-value=0.31).

This lack of significant difference in progression-free survival justifies the design of our economic analysis. Thus, a cost-minimisation analysis considering similar effectiveness between the two regimens was performed from a French Public Healthcare System perspective. Our results support the assumption of comparable effectiveness. A significant cost increase was associated with the use of the bevacizumab plus paclitaxel regimen, in comparison with the bevacizumab plus docetaxel regimen. Treatment costs were approximately €60,200 and €53,100 respectively, with an approximate saving of €7,100 for the docetaxel-containing regimen. The drug costs did not differ between the two regimens (*p*-value=0.81) and represented around 80% of the total cost, mainly related to the use of bevacizumab. The high cost of bevacizumab added a significant economic burden to the health budget. The cost of generic compounds for docetaxel and paclitaxel was insignificant. This cost saving of €7,100 in favour of the bevacizumab plus docetaxel regimen was explained by a decreased need for both hospitalization linked to chemotherapy administration, and healthcare travel: once (on day 1) every 21 days and three times (on days 1, 8 and 15) every 28 days for the bevacizumab plus docetaxel regimen and bevacizumab plus paclitaxel regimen, respectively (whereas the length of chemotherapy treatment is the same). Controlling healthcare travel prescription and expenses is an important issue in regulating the French Social Security System's finances. Health authorities are currently advised to reduce healthcare travel expenditures. Choosing the regimen bevacizumab plus docetaxel allows a 40% decrease in healthcare travel costs.

The results of the present study need to be viewed within its limited context: a retrospective analysis with small sample size. Medical indirect and intangible costs were not taken into account. Patient choice and quality of life were not included in this study. These two criteria cannot be measured in a retrospective study, although they are crucial when comparing palliative chemotherapy regimens. However, it is quite likely that reducing both hospitalization for chemotherapy administration and healthcare travel would improve a patient's quality of life.

Despite these limitations, the results of our study are representative of routine practices. Taking into account the patient profile (young women with good performance status and hepatic function), the choice of first-line bevacizumab plus taxane-based chemotherapy should lead to cost saving as compared to bevacizumab plus docetaxel-based chemotherapy; but bevacizumab is funded only in first-line treatment of mBC with paclitaxel-based chemotherapy (15-16). However, it is interesting to extrapolate our results to the national population with HER2-negative mBC. Each year, around 130 patients with HER2-negative mBC are treated by bevacizumab plus taxane-based chemotherapy in first-line chemotherapy in the Franche-Comté region, and historically, around 40% of patients by the bevacizumab plus docetaxel regimen. The Franche-Comté region represents around 1.5% of all patients treated for mBC in France. Thus, the potential switch from the bevacizumab plus paclitaxel to bevacizumab plus docetaxel could ensure the French Public Healthcare System a cost saving of €24,000,000 [calculation=130 patients × 0.40 (% bevacizumab plus docetaxel use) × €7,100/0.015 (%)]. Nationwide, this potentially significant saving could be used to finance the use of new innovative and expensive antineoplastic drugs (such as albumin-bound paclitaxel (ABRAXANE®) and to optimize consumption of healthcare system resources.

In conclusion, whereas bevacizumab is recommended for first-line treatment of mBC with paclitaxel-based chemotherapy, our economic analysis has shown that the bevacizumab plus docetaxel regimen is the most cost-efficient regimen. Bevacizumab plus docetaxel-based chemotherapy could be an attractive option for the French Public Healthcare System, with a potential cost saving of €24,000,000 per year. In the context of current health policy, with most governments trying to limit the escalation of healthcare expenditure, it is necessary to find strategies that are as effective but less costly. Our economic analysis may contribute to the on-going debate about the availability and use of innovative chemotherapy drugs.

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