Burden of breast cancer with brain metastasis: a French national hospital database analysis

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Original article
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Abstract

Objective:
Incidence of breast cancer with brain metastases (BCBM) is increasing, especially among patients over-expressing HER2. Epidemiology on this sub-type of cancer is scarce, since cancer registries carry no information on the HER2 status. A retrospective database analysis was conducted to estimate the burden of BCBM, especially among HER2-positive patients in a secondary objective.

Methods:
Patients with a new diagnosis of BCBM carried out between January and December 2008 were identified from the national hospital database using the International Disease Classification. Patients receiving a targeted anti-HER2 therapy were identified from the national pharmacy database. Hospital and pharmacy claims were linked to estimate the burden of HER2-positive patients. Data on hospitalizations were extracted to describe treatment patterns and healthcare costs during a 1-year follow-up. Predictors of treatment cost were analyzed through multi-linear regression analysis.

Results:
Two thousand and ninety-nine BCBM patients were identified (mean age (SD) = 57.8 (13.6)), of whom 12.2% received a targeted anti-HER2 therapy; 79% of patients had brain metastases associated with extracranial metastases, and the attrition rate reached 82%. Patients received mostly palliative care (47.4%), general medical care (40.6%), and chemotherapy (35.0%). The total annual hospital cost of treatment was 8,426,392€, representing a mean cost of 22,591€ (±14,726) per patient, mainly influenced by extracranial metastases, surgical acts, and HER2-overexpression ($p < 0.0001$).

Conclusions:
The database linkage of hospital and pharmacy claims is a relevant approach to identify sub-type of cancer. Chemotherapy was widely used as a systemic treatment for breast cancer rather than for local treatment of brain metastases whose morbi-mortality remains high. The variability of treatment costs suggests clinical heterogeneity and, thus, extensive individualization of protocols.

Introduction

Breast cancer (BC) is the second primary tumor responsible for the development of brain metastases (BM)[1,2]. The incidence of BM is increasing due to advances in diagnosis and improvement of treatments which change the natural history of the disease. BM are frequent, occurring in 10–16% of metastatic breast cancer (MBC)[3], especially for patients who over-express the Human Epidermal growth factor Receptor 2 (HER2+). The HER2-oncoprotein was identified as a predictive factor of BM[4], but data on this sub-population are scarce, as French cancer registries carry no information on the HER2 status. Ten-to-30% of BC patients over-express the HER2-oncoprotein[5,6], but the efficacy of therapies targeting HER2 may have changed the clinical course of this sub-set of patients. Because

of their intracranial localization, BM result in important functional disorders such as headaches, altered cognitive or motor functions, psychological disorders, and seizures[7]. Therapeutic management can be ablative, such as surgery or stereotactic radio-surgery, depending mainly on the number of intracranial metastases. For multiple BM, whole-brain radiotherapy is considered the treatment of reference[3,8]. Chemotherapy is generally used in addition to these reference treatments as a systemic treatment, and is a source of important healthcare costs which have not been extensively evaluated. Indeed, more than 70% of patients with HER2-positive breast cancer with brain metastases (BCBM) are also affected by other extracranial metastases[9,10]. Major side-effects such as hair loss or transient worsening of neurological symptoms are associated with classical treatments for BM that may have a major impact on patients' quality-of-life.

The medical need for effective treatments of BM is still unmet and contributes to the high morbidity and poor prognosis associated with this disease[3,8]. Chemotherapy is not considered as an effective standard treatment for BM because most chemotherapeutic agents do not cross the blood–brain barrier to deliver active substance at the tumor site. Nevertheless, the role of chemotherapy is increasingly debated and studied[7,11–15]. Recent data from clinical trials suggest that new oral drugs with a low molecular weight are able to cross the blood–brain barrier and may be effective for treating BM[16–19]. However, the sub-population likely to benefit from these new treatments remains poorly defined. Epidemiological as well as economic data on BCBM are scarce and fragmentary. Further data are needed to improve understanding of the size and the needs of this population. With the emergence of new oral drugs, it is necessary to estimate the healthcare costs associated with classical treatments and to understand its predictors, especially in an economic environment increasingly constrained.

The availability of exhaustive national hospital and pharmacy claims data in France provides an opportunity to assess the burden of BCBM more completely and to estimate the sub-population of HER2-positive patients which is specifically treated with anti-HER2 therapy. The first objective of our study was to estimate the burden of BCBM and the second, the burden of HER2-positive patients with BCBM. Data were collected on incidence, current treatment patterns, and hospital healthcare costs related to their management.

Patients and methods

Study design and data source

A retrospective cohort analysis of BC patients within their first year of a BM diagnosis was conducted using French national hospital and pharmacy claims recorded between 2006–2009. The hospital claims database contains medico-administrative information registered in the patient medical records during 1-day hospital stays (i.e., outpatient hospitalizations) and conventional hospital stays (i.e., inpatient hospitalizations). The pharmacy claims database contains all expensive innovative drugs delivered during each hospitalization that are paid to hospitals by the Health Insurance in addition to the per-case payment. Since 2008, hospitalizations can be linked to pharmacy claims, but only for public hospitals and non-profit private hospitals involved in public hospital duties. This last hospital category includes cancer treatment centers. This new linkage system allows analyzing expensive drug exposure during hospital stays for a given patient, thanks to a unique anonymous patient number.

Selection of the study population and time of follow-up

Patients included in the study were selected from the national hospital claims database using the diagnostic codes of the 10th Revision of the International Classification of Diseases (ICD-10)[20]. Inclusion criteria were cumulative (Figure 1):

 (i)   Female with a primary or secondary diagnosis of BC (C50);
 (ii) Who developed secondary BM (C79.3) between 01/01/2008 and 12/31/2008 (i.e., inclusion period), including BM only (without extracranial metastases) as well as BM associated with extracranial metastases (i.e., bone, lung, lymph node, skin and liver metastases);
(iii) Who had no previous BM from 2006–2007 (i.e.; newly diagnosed for BM); and
(iv) Who were treated in public hospital.

The claims data from 2006–2007 were used to check if patients had a prior hospitalization for BCBM to the inclusion period (01/01/2008 to 12/31/2008). Thus, patients with a hospitalization for BCBM between 01/01/2006 and 12/31/2007 were excluded to fulfill the incidence approach of the analysis. Patients who were included were then followed over a period of 12 months from the date of their inclusion (i.e., date of the diagnosis of BM) until death or last news. For instance, a patient included in July 2008 was followed until July 2009, except if she died before the end of the follow-up period.

Hospitalizations not apparently linked to the BC diagnoses (5.7%) and hospitalizations with no patient identification number (6.5% and 1.8% of hospitalizations, respectively, in 2006 and 2009) were excluded from the database. Patients treated in private hospital were excluded since the information on expensive drugs was
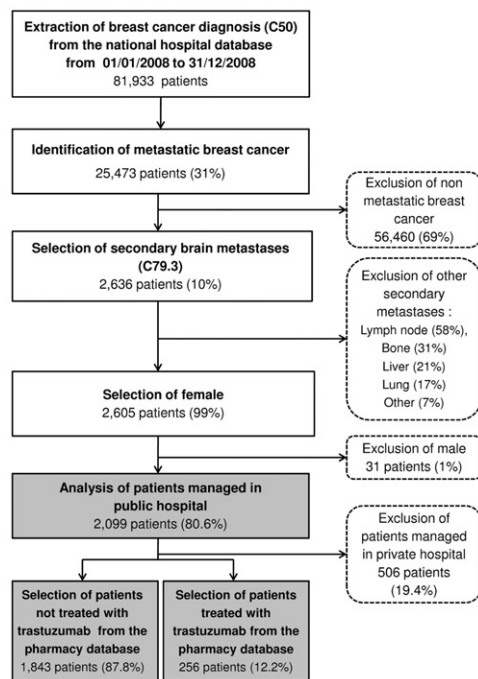
Figure 1. Algorithm used for the selection of the study population. The shaded boxes indicate the patient groups analyzed.

not available for these hospitals (i.e., clinics and private centers).

The study cohort was divided into two groups of interest: not trastuzumab treated patients (Group 1) and trastuzumab treated patients (Group 2). The prescription of trastuzumab, a targeted therapy for HER2-positive patients, was used as a surrogate marker for the HER2+ status. The data collected for each patient were anonymous. Since the study was a retrospective analysis of databases, no further specific authorization was required. *HEVA* (a Contract Research Organization) holds an authorization to extract data from the French hospital and pharmacy claims databases (Authorization CNIL n°1419102).

Cost data and statistical analyses

Costs were estimated from the Health insurance perspective using the national tariffs published in the *French Official Journal*. Cost analysis included direct medical costs related to treatments occurring in hospital setting (i.e., chemotherapy, radiotherapy, surgery, general medical care, para-clinical care, and palliative care). Costs were calculated over a 1-year period. The cost of treatment per patient (y) included the number of hospitalizations (n_h), the per-case payment including physician's fees (C_s), costs related to additional billing for intensive care

or resuscitation (C_{sup}), and costs of expensive drugs (C_{ed}) adjusted for the dose administered (Q):

$$y = (n_h \times C_s) + (C_{sup.}) + (C_{ed} \times Q).$$

Descriptive analyses were conducted on the main characteristics of the study population (age, duration of follow-up, metastatic localization, and treatment patterns), and on costs description (distribution). Mean, standard deviation (SD), range, and percentage were calculated. Patients characteristics between group 1 and group 2 were analyzed using ANOVA test for mean comparison and Fisher's exact test for frequency comparison. Multi-linear regression analyses were conducted on clinical and economic variables to identify the predictors of the mean cost of treatment in each patients group. The following variables were included in the model: mean age, metastatic localization (BM only, BM associated with one extracranial metastasis, BM with multiple extracranial metastases) and treatment pattern (chemotherapy, radiotherapy, surgery, general medical care, para-clinical care, palliative care, expensive innovative drugs, and other treatments). Differences were considered significant at a 5% level. All statistical analyses were performed using the SAS® Software 9.2.

Results

Baseline patients' characteristics

A total of 2,099 patients with BCBM were included. The median age at diagnosis was 60.0 years (range: 20–98). Groups 1 and 2 accounted for 87.8% and 12.2% of the study population, respectively. Most patients suffered from BM associated with extracranial metastases (79.0%), while 21.0% presented BM only. At the end of the 12-months follow-up period, 84.1% of patients with BCBM had either died or returned home (Table 1). The number of patients had decreased from 2,099 (100%), 791 (37.7%), 507 (24.1%) to 371 (17.7%) at 3, 6, 9, and 12 months, respectively.

Treatment patterns

During the first year following their diagnosis of BM, patients received palliative care (47.4%), general medical care (40.6%), and chemotherapy (35.0%). Radiotherapy and surgery accounted, respectively, for 21.7% and 7.2% of the medical care received (Table 1). Local treatment (i.e., surgery and radiotherapy) were mostly used within the first months (Figure 2). Among the study population, 34.0% of patients received at least one expensive drug therapy. Thirty-seven different expensive innovative drugs were prescribed. Drugs identified in the pharmacy claims database were administered for systemic treatment of BC in

Table 1. Characteristics of the study population.

Population (n, %)	Total (n = 2,099)		Group 1 (without trastuzumab) (n = 1,843)		Group 2 (with trastuzumab) (n = 256)		p-value
Age at diagnosis							
Mean (SD)	57.8	(13.6)	58.5	(13.6)	52.5	(12.5)	<0.001
Median	60.0		60.0		50.0		
Range	20–98		20–98		20–90		
Duration of follow-up, months							
Mean (SD)	3.6	(4.1)	2.9	(3.7)	8.1	(4.3)	<0.001
Median (Min–Max)	1.4	(0–12)	1.1	(0–12)	10.0	(0–12)	
Localization of metastases							
Brain metastases only	440	21.0%	414	22.5%	26	10.2%	<0.001
Brain metastases associated with extracranial metastases:	1,659	79.0%	1,429	77.5%	230	89.8%	<0.001
Multiple[a]	915	43.6%	784	42.5%	131	51.2%	
Liver	360	17.2%	315	17.1%	45	17.6%	
Bone	219	10.4%	189	10.3%	30	11.7%	
Lung	78	3.7%	69	3.7%	9	3.5%	
Lymph node	56	2.7%	44	2.4%	12	4.7%	
Other	31	1.5%	28	1.5%	3	1.2%	
Patient's destination at the end of follow-up period							0.006
Death and return home[b]	1,765	84.1%	1,529	83.0%	236	92.2%	
Post-acute rehabilitation unit	180	8.6%	166	9.0%	14	5.5%	
Acute care unit	107	5.1%	102	5.5%	5	2.0%	
Home hospitalization	23	1.1%	22	1.2%	1	0.4%	
Long-term care unit	23	1.1%	23	1.2%	0	0.0%	
Psychiatric institution	1	0.0%	1	0.1%	0	0.0%	
Treatment pattern							<0.001
Chemotherapy[c]	735	35.0%	510	27.7%	225	87.9%	
General medical care[d]	852	40.6%	760	41.2%	92	35.9%	
Palliative care	995	47.4%	920	49.9%	75	29.3%	
Radiotherapy	455	21.7%	381	20.7%	74	28.9%	
Surgery	151	7.2%	130	7.1%	21	8.2%	

[a]More than two extracranial metastases localizations.
[b]In 2008, the information on 'death' and 'return home' was coded in the hospital database as a single variable entitled 'death or return to home'. The distinction between 'death' and 'return to home' has only been available since 2009.
[c]Expensive innovative drugs are excluded.
[d]Medical care included follow-up explorations and physician consultations.

88.0% of the patients. One drug (fotemustin) was approved for the treatment of BM and was prescribed to 0.4% of patients (3/713), and 12.6% of patients had drugs approved for other malignant tumor (i.e., lymphoma, colorectal cancer, . . .).

Treatment costs and predictors

The mean annual cost of treatment per patient was 22,591€ (±14,726) and was significantly higher for patients treated with trastuzumab (29,995€ ± 13,484) than for patients not treated with trastuzumab (18,039€ ± 13,587) ($p < 0.001$) (Table 2). The 1-year hospital cost of management of the whole population was 8,426,392€. Expensive drugs accounted for 44.8% of the mean annual cost of treatment per patient. An important variability of costs has been noticed, especially for chemotherapy and palliative care treatments (Figure 3). Main cost drivers were surgery ($p < 0.0001$), extracranial

metastases associated with BM ($p < 0.0001$), and the HER2-positive status ($p < 0.0001$) (Table 3).

Discussion

This study presents data on epidemiology, treatment patterns, and hospital costs of BC over the first year following the diagnosis of BM using the French hospital and pharmacy claims databases from 2006–2009, and provides the first data on the sub-population of HER2-positive patients at a population level.

In our study population, 12.2% of patients were assumed to be HER2+, which is consistent with the available literature[21,22]. Nevertheless, we should notice that, despite the implementation of HER2 biological marker diagnosis into routine clinical practice, a slight proportion of patients may have an indeterminate status and, thus, are not treated with targeted therapy (i.e., technical diagnosis

failure, changes of serum HER2 status during clinical course). The second factor contributing to under-estimate the HER2+ population may be due to patients who cannot be treated with trastuzumab because of contraindications or severe side-effect (i.e., cardio toxicity) requiring a change of treatment (0.24% according to Horiguchi et al.[23]). The third reason may be due to patients or clinicians who may refuse the intravenous administration of chemotherapy, preferring the oral route of administration, and which are excluded from hospital care[24]. So far, the availability of database linkage between hospital and Health Insurance claims, that includes consumptions of non-hospital care, do not allow analyzing the full course of healthcare.

Despite those limitations, epidemiological findings are consistent with data reported by previous studies. The diagnosis of BMs was often associated with extracranial metastases (79.0% of BCBM patients), as reported in a previous retrospective study (74%, $n = 207$)[10]. Despite the absence of survival data, results indicate that, after

12 months of follow-up, 84.1% of patients were reported to have died or to have returned home. If we consider the high morbidity on this sub-type of cancer, there is a high probability that the percentage of patients who returned home is marginal compared to the percentage of death. This finding is consistent with a literature review (2004) suggesting a 20% survival rate in BCBMs after 1-year of follow-up[3], and with the median survival time reported in the literature (2–16 months)[25,26].

Most frequently used chemotherapeutic regimens are consistent with those reported previously reported (i.e., paclitaxel, docetaxel, vinorelbine[7]). Chemotherapy was offered to 35% of patients in our cohort, while the use of radiotherapy, which is the standard treatment of BM, was only used for 21.7% of patients and appeared lower than the rates having been reported by others[8,25]. Indeed, radiotherapy sessions are conducted principally in the private sector (50% in a previous survey and from the *Statistique Annuelle des Etablissements* database[27]), and therefore are not identifiable through the public hospital claims database.

The difference of mean costs between the two groups may be due to the use of trastuzumab, which accounted for
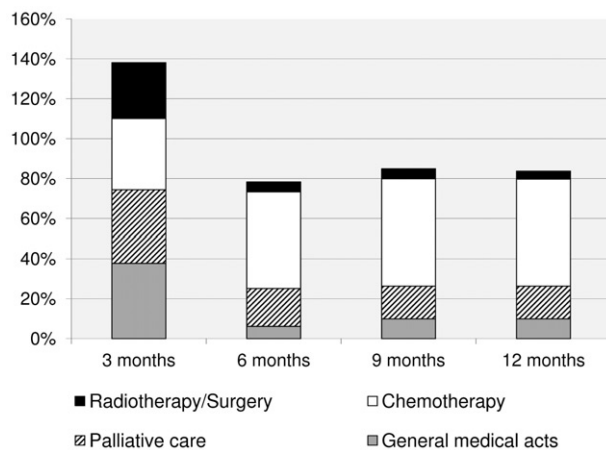

Figure 2. Distribution of treatment use during the 1-year follow-up period for the whole population ($n = 2,099$). This figure presents the distribution of treatment use by 3-month period. For instance, at 3 months of follow-up, 38% of patients had received general medical care, 37% palliative care, 36% chemotherapy and 28% radiotherapy and surgery. The total exceeds 100% since patients may have received one or more types of treatments over the period. Expensive innovative drugs are included in the category *chemotherapy*.
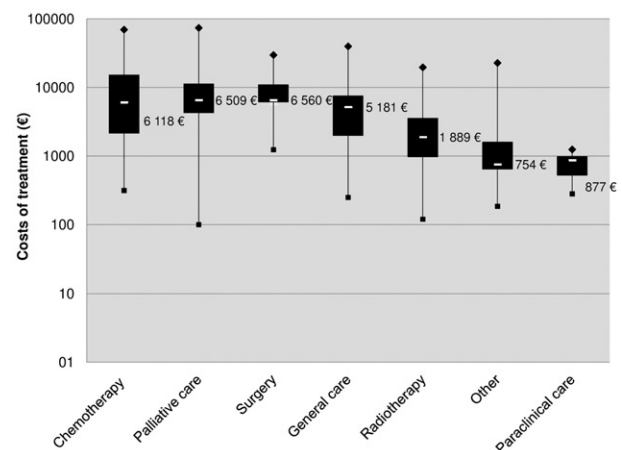

Figure 3. Box and whisker plot of the distribution of healthcare costs ($n = 2,099$). The cost shown on the graph is the median cost per treatment category. From top to bottom of the graph: the largest observation (♦), the upper quartile, the median (–), the lower quartile and the smallest observation (■).

Table 2. Healthcare costs over 1 year of follow-up.

Mean annual cost per treatment category (€), SD	Total ($n = 2,099$)	Group 1 Patients not treated with trastuzumab	Group 2 Patients treated with trastuzumab
Chemotherapy	14,523 ± 14,732	9,090 ± 12,257	23,363 ± 14,157
Surgery	1,044 ± 3,267	1,195 ± 3,684	800 ± 2,434
Radiotherapy	945 ± 2,154	954 ± 2,264	931 ± 1,972
General medical care	2,606 ± 4,467	2,809 ± 4,612	2,275 ± 4,216
Palliative care	2,919 ± 6,096	3,591 ± 6,829	1,826 ± 4,476
Total	22,591 ± 14,726	18,039 ± 13,587	29,995 ± 13,484

Table 3. Multivariate regression analyses performed on the mean cost of treatment.

R-Square = 0.36 Parameters	Estimate	Standard Error	95% Confidence Interval		p
Age	−0.0005	0.0008	−0.0020	0.0011	0.5392
Metastatic localization:					
BM only	0.0000	–	–	–	–
BM + one extracranial localization	0.0788	0.0293	0.0213	0.1363	0.0072
BM + multiple extracranial localization	0.1519	0.0292	0.0946	0.2092	<0.0001
HER2 status (trastuzumab vs no trastuzumab)	−0.5797	0.0344	−0.6472	−0.5122	<0.0001
Treatment pattern:					
Chemotherapy	−0.2446	0.0341	−0.3114	−0.1778	<0.0001
Surgery	−0.5517	0.0414	−0.6329	−0.4706	<0.0001
General medical care	−0.1867	0.0235	−0.2328	−0.1406	<0.0001
Palliative care	−0.2475	0.0254	−0.2974	−0.1976	<0.0001
Para-clinical care	−0.2881	0.1664	−0.6142	0.0380	0.0833
Expensive innovative drugs	−0.2628	0.0299	−0.3214	−0.2042	<0.0001
Mean duration of stay	0.0015	0.0010	−0.0005	0.0036	0.1434

57.2% of the overall cost of expensive drugs after a 12-month follow-up. On the whole, the mean cost of treatment reported in our study is difficult to compare with the literature, since studies analyze different costs components and different types of advanced BC, not restricted to BCBM[28–31]. Drug tariffs vary also from one country to another, depending on the healthcare system, and may contribute to variability in the costs reported. Nonetheless, our results are consistent with those reported by Pelletier et al.[32]. From a US claims data analysis, they reported a mean annual cost of 23,738$ per patient for hospitalizations within an incident cohort of BCBM. Finally, we found marked variability in hospital costs between and within treatment categories, especially for chemotherapy and palliative care. Clinical heterogeneity between patients and the widespread use of individualized therapeutic protocols for metastatic stage may contribute to the inherent variability in cost analysis.

Nevertheless, this study shares the typical limitations of claims database analysis. First, the number of BCBM cases may be under-estimated due to misclassification or incomplete reporting of BM diagnoses related to BC. Nonetheless, missing data decreased over the period 2006–2009, suggesting an improvement in the quality of hospital data collection. Our economic evaluation was limited to hospital costs, since information on non-hospital costs was not available (e.g., home nursing, oral drugs). These costs are assumed to be important, due to the increasing proportion of patients with cancer who are cared at home[33]. Finally, the estimation of expensive drug costs was conducted using national tariffs, which do not necessarily exactly reflect the actual costs of drugs. The latter may vary from hospital-to-hospital, depending on agreements reached between hospital pharmacies and wholesalers. No data on the mismatch between actual costs and published tariffs is available. Direct non-medical costs (i.e., medical transportation, lost wages) would also be important to estimate in future analyses from a societal perspective. BCBM have an impact on patient's quality-of-life and costs supported by the patient's family could be high, especially for the end-of-life care.

Despite those limitations, the use of a national database is a relevant approach at several levels. The claims database ensures representativeness of the analyzed population since data are collected from all hospitals, in contrast to the prospective studies performed in selected centers, not necessarily representative of national treatment norms. Secondly, specific patient groups often excluded from clinical trials could be analyzed in such database (i.e., elderly patients or patients with comorbidities). Thirdly, hospital and pharmacy claims studies are used by the health authorities for tracking reimbursement objectives. As a result, data on resource utilization are entered systematically into databases, allowing collection of good quality data and minimizing the risk of under-reporting of costs due to mis-coding. It should also be noted that, in France, regulatory measures ensure, in principle, equal access to innovative drugs for all patients. Therefore, the estimation of populations treated with these drugs is assumed to be relatively exhaustive and consistent with national healthcare practice.

Conclusion

Several randomized and observational studies have described the burden of BCBM, but, so far, no data were available at a population level. Our findings confirm that hospital and pharmacy claims data could be a relevant alternative to a typical epidemiological database such as cancer registries. In addition, these results highlight the lack of chemotherapeutic alternative to radiotherapy and surgery for the local treatment of BM. Given the high morbi-mortality, there is a critical medical need to develop effective therapies to treat or to prevent the occurrence of BM. In patients whose prognosis is in any case poor, the

choice of chemotherapy over supportive and palliative care, or conversely, has cost consequences, for which responsibility should be shared between patients, physicians, and stakeholders.

Transparency

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