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Research article

A multi-center evaluation of clinical pathways cost and time using real-life data in patients treated for their breast cancer by Trastuzumab intravenous and subcutaneous in day sessions

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Abstract

Introduction: Trastuzumab (Herceptin®), a monoclonal antibody and targeted therapy, is indicated for the treatment of adult patients with breast cancer overexpressing the HER2 receptor. There are two forms of administration, intravenous (IV) and subcutaneous (SC). The objective of the study is to evaluate the organizational and economic impacts generated by the administration of the SC versus IV form. Methods: An observational and multicenter study in patients with breast cancer overexpressing HER2. For one month (14/11/2016 to 15/12/2016, 9 healthcare facilities consecutively included patients among their active file. A comparative SC versus IV analysis (Pearson's Chi-two test and Student's T-test, 0.05 significance threshold) was conducted on the following criteria: (1) preparation time by pharmacy, (2) pathway time during administration and (3) economic evaluation of consumable costs for preparation and administration. Results: 411 patients were included, 245 (60%) for the SC group and 167 (40%) for the IV group. SC preparations are on average 12 minutes significantly shorter than IV preparations (p <10-4). The care pathway for SC administration is on average 107 minutes significantly shorter than IV (p <10-4). The cost of consumables for a SC pathway is significantly lower by 11.07 € HT (p <10-4) compared to IV. Conclusion: This multicentric study highlights the benefits for patients (pathway time) and for care centers (costs) of trastuzumab SC administration compared to the IV form.

Keywords: HER2-positive breast cancer, observational study, trastuzumab, care pathway, medico-economics.

Introduction

Breast cancer is the most common cancer in women [1]. An aggressive form of breast cancer overexpressing the HER2 receptor has for reference treatment trastuzumab [2–4]. (Herceptin®, F. Hoffmann-La Roche Ltd, Bâle, Suisse), currently available under 2 formulations : trastuzumab 150 mg, available as a powder for concentrate for solution for infusion in intravenous administration (IV) and trastuzumab 600 mg, ready-to-use solution for subcutaneous administration (SC).

Trastuzumab can only be used in patients whose tumors have HER2 overexpression, representing about 12% of breast cancers. When administered intravenous, the recommended initial loading dose of trastuzumab is 8 mg / kg body weight over a period of approximately 90 minutes, followed by 6 mg / kg body weight every 3 weeks. If the initial dose has been well tolerated, the recommended maintenance dose may be given as a 30-minute infusion. When administered by subcutaneous injection, the recommended dose is 600 mg, regardless of the patient's body weight. No loading dose is required. This dose should be administered subcutaneously for 2 to 5 minutes every 3 weeks.

Trastuzumab subcutaneous formulation has been marketed in France for the treatment of adult patients with HER2 positive breast cancer since September 2014. Various clinical studies have shown the non-inferiority of trastuzumab SC versus trastuzumab IV in terms of efficacy and safety of administration [5-6]. The HannaH [5] study, performed in a neo-adjuvant and adjuvant setting, demonstrated the non-inferiority of the SC formulation vs. the IV formulation in terms of complete pathological response (pCR) and pharmacokinetics (serum residual concentration at the pre-dose of cycle 8). The HannaH study concluded that the efficacy of the SC formulation is comparable to that of the IV formulation (8 mg / kg loading dose then 6 mg / kg maintenance dose).

The PrefHer study [6] evaluated in a randomized trial, the preference of patients with HER2-positive breast cancer, after having tested the 2 routes of administration. The study concluded that there was a preference for SC formulation versus IV formulation. MetaspHer Study [7] assessed patient preference for either the SC or IV formulation in the treatment of HER2-positive metastatic breast cancer patients responding to front-line treatment trastuzumab IV combined with chemotherapy for at least 3 years. This study is still ongoing and is assessing as secondary and exploratory criteria, tolerance, preference of health professionals, patients' quality of life, progression-free survival and overall survival. The primary endpoint analysis concluded that there is an administration preference for the SC formulation.

In addition to these trials, this study focuses on the organizational aspect of the management of patients with the objective to quantify the benefits of the administration of trastuzumab IV and SC formulations, respectively for patients with HER2-positive breast cancer (pathway time) and for care centers (cost of administration).

Methods

Study design

This observational and multicenter study (9 centers) was conducted through the collection of 2 types of data: (a) a questionnaire to be completed for each center to collect data on the organizational model for the management of patients with HER2-positive breast cancer (all stages) treated with trastuzumab (IV or SC); (b) a questionnaire to be completed for each patient to anonymously collect the different pathways characteristics of the patient with HER2-positive breast cancer treated with trastuzumab (IV or SC). The collection period was 1 month from November 14, 2016 to December 15, 2016. The table 1 lists the 9 centers.

A sampling plan defined the minimum number of patients to be recruited for all 9 centers. The main endpoint used to determine the size of the two arms was the time spent by the patient during a chemotherapy session, as reported in the study "Time Savings with Trastuzumab Subcutaneous Vs. Intravenous administration: a time and motion study "[8]. The minimum number of patients to be included in each arm was 135 (15 per center). Patients were consecutively included from the active list of patients undergoing treatment in the day hospital service of each center.

Assessment criteria of care pathway

The objective of the study is to evaluate organizational and economic impacts generated by the administration of trastuzumab SC versus IV formulation. For the evaluation, 3 main criteria were selected: (1) preparation time of trastuzumab by the pharmacy, (2) total patient pathway time during administration and (3) consumables costs for preparation and administration of trastuzumab. These 3 criteria were evaluated by considering all the tasks related to the preparation (Figure 1) and the administration (Figure 2). Figure 1 shows the two possible preparation circuits, according to IV or SC formulation and the associated tasks. Steps of patient pathway are common to both formulations (see generic pathway in Figure 2). However, the pathway of each patient does not necessarily include all the described steps, some of which are specific to patient's state of health.

In addition to pathway steps, seven additional characteristics were collected for each patient: age (in years), weight (in kg), trastuzumab formulation (SC or IV), treatment combination (monotherapy or combination with another IV treatment), presence of a dedicated SC circuit (yes / no), level of anticipation of trastuzumab preparation

Table 1. Number of patients for IV and SC groups in each center

Centers	Type of centers	Patients, n				
		SC formulation		IV formulation		Total
		n	%	n	%	n
Centre Antoine Lacassagne (Nice)	CLCC	25	36%	44	64%	**69**
Clinique Pasteur (Toulouse)	HP	67	100%	0	0%	**67**
Polyclinique de Gentilly (Nancy)	HP	44	72%	17	28%	**61**
CHR d'Orléans	CHU	18	37%	32	65%	**49**
CHRU Tours Hôpital Bretonneau	CHU	17	38%	28	62%	**45**
Centre Hospitalier de Bretagne Sud (Lorient)	CH	20	57%	15	43%	**35**
Institut Hospitalier Franco-Britannique (Levallois-Perret)	ESPIC	22	67%	11	33%	**33**
Institut Bergonié (Bordeaux)	CLCC	15	50%	15	50%	**30**
Centre Jean Perrin (Clermont-Ferrand)	CLCC	17	77%	5	23%	**22**
TOTAL		**245**	**60%**	**167**	**41%**	**411**

CLCC: Center for the fight against cancer

HP: private hospital

CHU: University hospital center

CH: Hospital center

ESPIC: Private health institution of collective interest

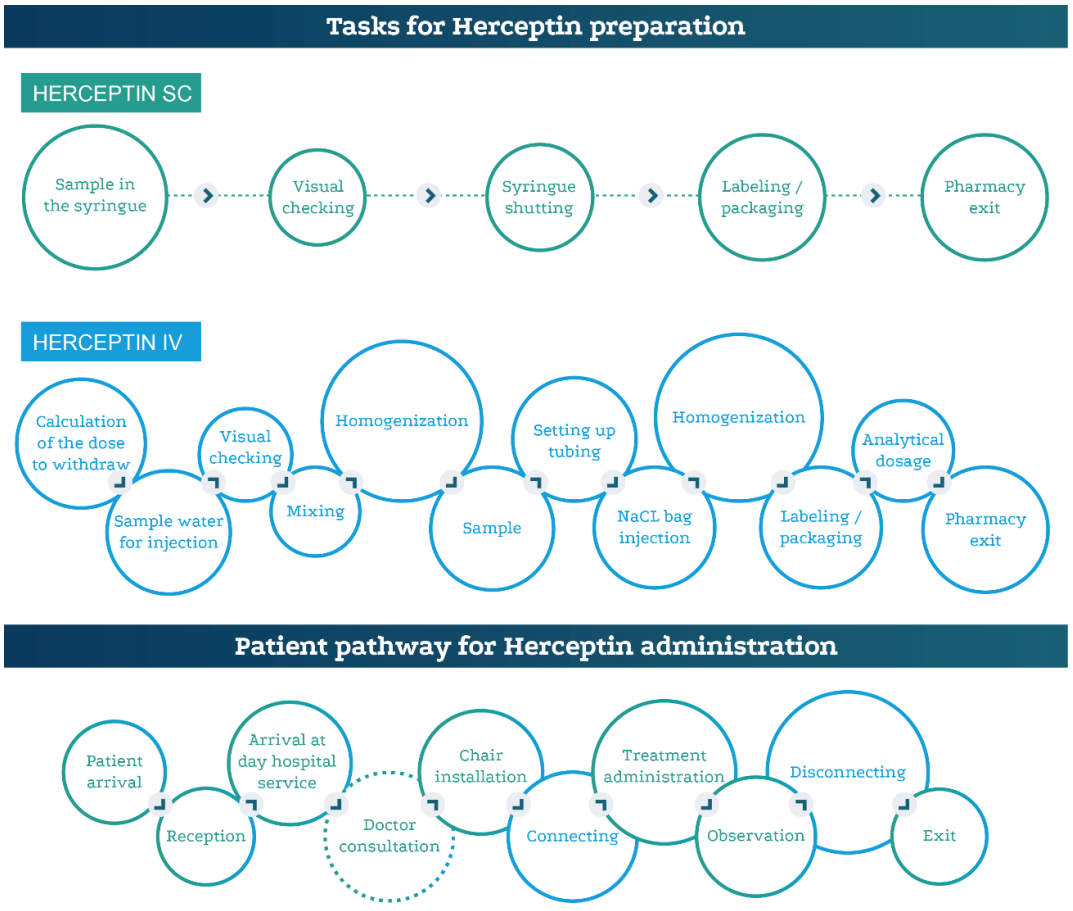

Figure 1. (a) Chronological sequence of tasks for trastuzumab preparation at the pharmacy. The pathway is different according to the formulation to be administered (IV or SC); (b) Chronological sequence of patient pathway steps for trastuzumab administration. This pathway is generic for IV and SC formulation and allows to describe all the possible steps. NB: All the steps do not necessarily take place for all patients.

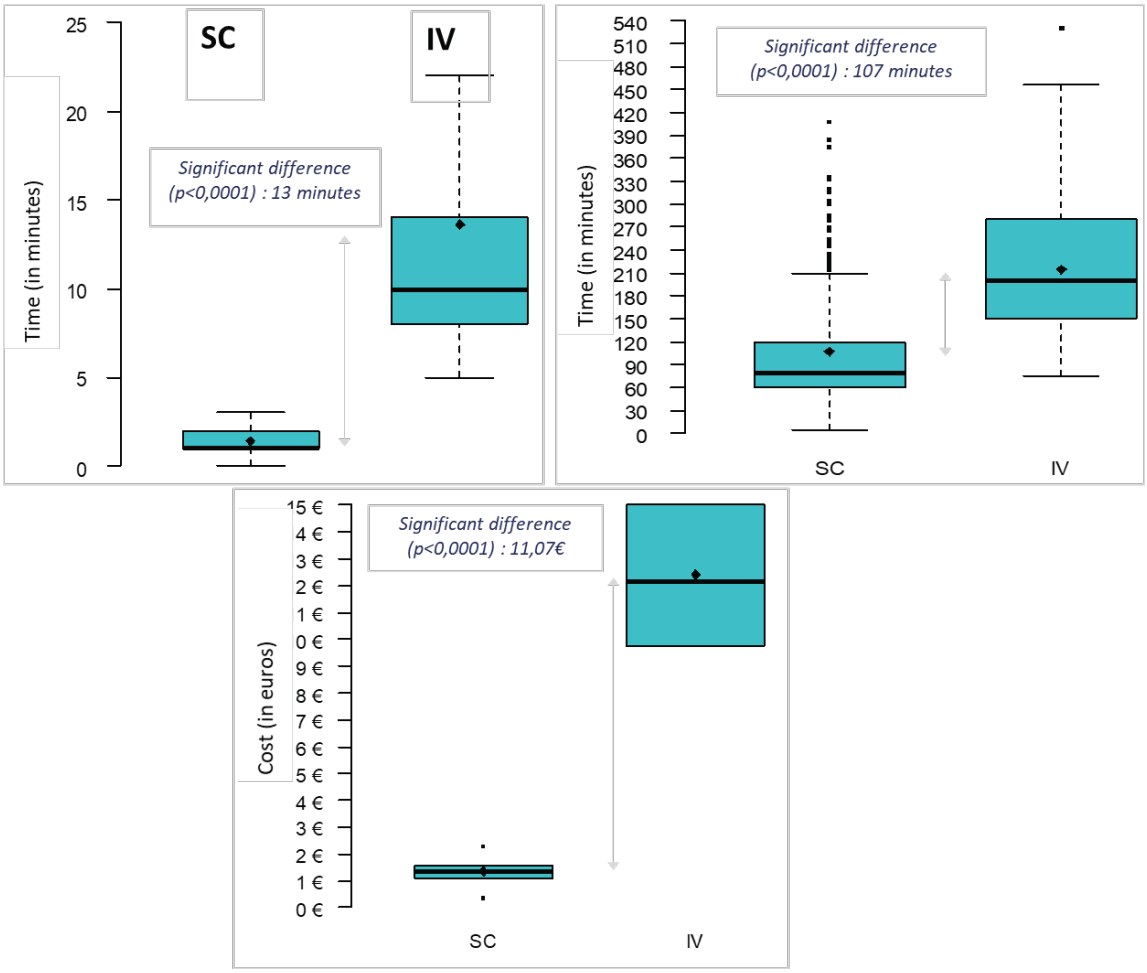

Figure 2. SC versus IV formulation comparative analysis: (a) preparation time, (b) total patient pathway time, (c) consumables costs for preparation and administration of trastuzumab

(100% anticipated / partially / without anticipation), the time of each step of the pathway (see Figure 2, in minutes).

In order to ensure the validity of the real-life data collection criteria, a committee of 9 medical experts from each center has been set up. The content of the questionnaires has been validated by this committee. The third evaluation criterion, consumables cost, was also detailed by consumable. Thirteen different consumables are included in the analysis (infusion set, Y-site infuser, 30 ml luer lock syringe for preparation, secure Huber needle, 3-way luer lock valve, 10 ml luer lock syringe for preparation, NaCI 250 ml, disconnection set, 18G needle for preparation, secure administration device (Duoperf® type), 50ml NaCl purging bag 0.9%, Needle for SC 23G, Stopper). For each consumable, the unit cost (excluding taxes) and the quantity used have been collected in the "center" questionnaire. The advantage of this economic evaluation is its robustness as measurables consumables do not dependent of factors related to organization and characteristics of centers. It is also easily replicable and has no selection bias between the different centers.

Statistical analyses

SAS software was used to perform statistical analyses (Statistical Analysis Software, version 9.3, SAS Institute Inc., Cary, NC, USA). The descriptive analysis was carried out on the total population, then by subgroups (IV and SC), on all the collected criteria. The distribution of the variables was studied for the quantitative variables, and the frequencies for the qualitative variables. Comparisons between the two groups (IV and SC) were performed with parametric and non-parametric tests according to the distribution of the variables. The Pearson Chi-2 test (or Fisher exact test according to the distribution) was used for the qualitative variables, and the Student's T-test (or Wilcoxon distribution test) for the quantitative variables. All tests are bilateral. A p value < 0.05 was considered statistically significant throughout the analysis.

Identification of the characteristics explaining the mode of administration (IV / SC)

Univariate and multivariate logistic regressions analyses, with the dependent variable as mode of administration (IV / SC) and independent variables as age, weight of patients and the type of treatment (monotherapy or combination with another IV treatment) were performed. For each independent variable, the crude Odds Ratio (OR), the adjusted OR, and their 95% confidence intervals

were estimated.

Covariance analysis of the preparation and administration times of trastuzumab

The association between the preparation time of trastuzumab and the potentially explanatory factors of the preparation time (as identified in the above analyzes) was studied. Analysis by linear regression models made it possible to estimate for each candidate variable the crude association between the studied factor and the preparation time (univariate analysis).

A multivariate linear regression model was then used to study the adjusted association between the studied factor and the preparation time, all things being equal. The significance level chosen to include the variables in the multivariate analysis was 20%. Possible interactions between the various explanatory factors have also been sought. A step-down procedure was used to eliminate non-significant variables at the 5% threshold. The same analysis strategy was used to analyze the association between the trastuzumab administration time and the potentially explanatory factors of the pathway time as identified in the above analyzes. When data were not detailed per administration but only by center, mixed linear models adapted to the grouped data were used.

Results

Descriptive analyzes of the study population

Numbers

Among the 9 centers that participated in the study, 425 patient questionnaires were collected between November 14, 2016 and December 15, 2016 (1 month), of which 8 questionnaires were deleted due to duplication. The remaining 417 questionnaires describe the pathway of 411 patients (6 patients came twice for trastuzumab administration). The proportion of SC administration is 60% (245 patients, 248 sessions) and 40% (167 patients, 169 sessions) for IV (1 patient is counted in both groups because she received one SC administration and one IV administration). The details of the number of patients included in each center are presented in Table 1. A center (Clinique Pasteur) exclusively includes SC administrations. The repartition between SC and IV formulation depends strongly on center (respectively 77% -23% at Jean Perrin Center and 36% -64% at Antoine Lacassagne Center).

Age and weight

The average age of patients is 59 years (± 13): 60 years old (± 13) for patients with IV formulation and 58 years old (± 14) for patients with SC formulation. Mean patient ages are not significantly different between SC and IV groups (p = 0.0698). The average weight of the patients is 67 kg (± 14): 66Kg (± 13) for patients with SC formulation and 68Kg (± 16) for patients with IV formulation. Mean patient weights are not significantly different between SC and IV groups (p = 0.2812).

Modality of administration

Of the 417 chemotherapy sessions studied, 3% correspond to a first administration (13/413, 4 missing values). This rate is similar for IV (2%) and SC (4%) formulation. The proportion of administration of trastuzumab monotherapy is significantly different between the 2 formulations: 89% of the SC formulation sessions (221/248) are in monotherapy versus 39% of the IV formulation (66/169 sessions). Among the care centers, 3 dedicated SC organizations were identified: via dedicated chairs, via a dedicated time slot or via another unspecified organization. Twelve percent of all IV and SC sessions (50/417) were performed in a dedicated SC organization, that is to say 20% (50/248) of the SC sessions. The 50 sessions performed in SC dedicated circuit were observed in 4 of the 9 centers.

Comparative analyzes of care pathways

Indicator 1: Preparation time in pharmacy

The 5 tasks of trastuzumab SC preparation (Figure 1) were described in 74% of sessions (184/248). This rate increases to 80% if the steps "labeling / packaging" and “pharmacy exit” are pooled together. Regarding the preparation of trastuzumab IV, only 11% of the sessions (19/169) present the 12 tasks of preparation detailed in figure 1. "Analytical dosage" is reported in only 30% of sessions (51/169) and 25% of sessions (43/169) reported only the 2 tasks "start" and "end" of preparation (without any other details on tasks described in figure 1).

For the calculation of the total preparation time, the "pharmacy exit" task was excluded to avoid data over-dispersion due to the internal organization of the centers. In fact this task varies from few minutes after the preparation to an exit the day after. In addition, preparation time can’t be calculated for 75 sessions (18%) because of the quality of the data. The average total preparation time is 1 minute (± 1) for the SC formulation and 14 minutes (± 12) for the IV formulation. Average preparation times are significantly different between SC and IV groups (p <10-4) and significantly longer of 13 minutes (± 7) for the IV formulation (Figure 2a).

Indicator 2: Pathway time for administration

Of the 9 possible steps of trastazumab administration pathway (Figure 2), 4 are described in 90% of SC sessions: arrival, chair installation, administration and exit, and 2 other steps (connecting and disconnecting) are collected in 90% of IV sessions. The total average pathway time is 151 minutes (± 96): 108 minutes (± 75) for SC formulation and 215 minutes (± 87) for IV formulation.

These average pathways are significantly different between SC and IV groups (p <10-4), and significantly 107 minutes (± 80) longer for IV formulation (Figure 2b).

Indicator 3: Economic evaluation

The total cost of the consumables corresponds to the sum of the consumables used for preparation with those used for administration. For 29% of the sessions (121/417), this total cost can't be calculated (missing data). For the remaining 296 sessions (71%), the average cost is €5.27 excl (± 5.48): €1.35 excl (± 0.47) for SC formulation and €12.42 excl (± 2.20) for IV formulation. Average consumables costs are significantly different between SC formulation and IV formulation (p <10-4), with an average difference of €11.07 excl (± 1.36) (Figure 2c).

Analysis of explanatory factors (covariance)

The last part of the analysis focuses on the explanatory factors of the differences observed in the comparative analysis. These analyzes, univariate or multivariate, concern the 2 indicators of time (preparation and pathway), but not the consumables costs since this one does not depend on factors related to center's organization.

Analysis of the explanatory factors for preparation time

The univariate analysis (Table 2) shows that a trastuzumab SC preparation is on average significantly 12 minutes faster than an IV preparation (p <10-4). This gap decreases significantly when the rate of trastuzumab IV preparation increases (p = 0.0010), with equal administered formulation. For a 1% increase in the rate of trastuzumab IV preparation, the preparation time decreases by about 2 minutes on average.

Multivariate analysis (Table 2) shows that, on average, a SC preparation remains significantly 10 minutes faster than an IV preparation (p <10-4), with type of treatment and IV and SC preparation rates equal. A monotherapy treatment is on average significantly 2 minutes and a half faster that a combination therapy with another IV drug (p = 0.0176), with equal formulation and IV and SC preparation rates. The preparation time decreases significantly when the IV preparation rate increases (p = 0.0280), with equal formulation, type of treatment and SC preparation rate. The preparation time decreases significantly when the SC preparation rate increases (p = 0.0511), with equal formulation, type of treatment and IV preparation rate.

Analysis of explanatory factors for pathway time

The univariate analysis (Table 3) shows significant differences in average pathway time, without taking into account the influence of the other criteria: a SC pathway is 107 minutes faster than a IV pathway (p <10-4). In addition, at equal formulation, a monotherapy pathway is 82 minutes faster than a combination pathway (p <10-4) ; a pathway with a total anticipation is 65 minutes faster than a pathway without anticipation (p <10-4) ; a pathway within a dedicated SC circuit is one hour faster than a non-dedicated SC circuit (p <10-4) ; a pathway with a medical consultation is on average significantly 38 minutes longer that a pathway without (p <10-4).

The multivariate analysis (Table 3) shows that the following 6 care pathways remain on average significantly different, all things being equal (formulation, type of treatment, preparation, SC dedicated circuit, medical consultation): (1) a SC pathway is 54 minutes faster than IV (p <10-4); (2) a monotherapy pathway is 80 minutes faster than a combination pathway (p <10-4); (3) a pathway with partial anticipation is 23 minutes faster than an unprepared pathway (p = 0.0059); (4) a pathway with a total anticipation is 53 minutes faster than a pathway without anticipation (p <10-4); (5) a pathway with a dedicated SC circuit is 51 minutes faster than a non- dedicated SC circuit (p <10-4); (6) an administration pathway with a medical consultation is 33 minutes longer than a pathway without medical consultation (p <10-4).

Discussion

Our study highlights the benefit of using trastuzumab SC formulation compared to IV formulation, in accordance with previously published studies. On the one hand, trastuzumab SC preparation is on average significantly faster than IV preparation, which brings an organizational gain for the hospital center. On the other hand, SC trastuzumab administration pathway is on average significantly faster than IV trastuzumab administration pathway, which improves the quality of care for patients. Finally, the average cost of consumables is significantly less expensive by 89% for SC formulation compared to IV formulation. This study also shows the impact of organizational models on care pathway of patients. The positive impact of a dedicated SC circuit has been demonstrated.

To our knowledge, our study is the first multicenter observational study to address these two economic and organizational aspects in France. Previous studies were conducted based on patients enrolled in the PrefHer [8-10] clinical trial, therefore based on pre-screened patients and selected centers, used to clinical trials protocols. Some studies were monocentric observational studies and are therefore results are difficult to extrapolate [11,12]. A strong contribution of our study is the robustness and the reproducibility of the economic evaluation in several centers, and in all types of institution administering trastuzumab in France: centers for the fight against cancer (CLCC), university hospital center (CHU), hospital center (CH), private health institution of collective interest (ESPIC) and private hospital (HP). The other multicenter studies [13-15], studied a much smaller number of

Table 2. Association between trastuzumab preparation time and different factors

	Univariate analysis adjusted on formulation			Multivariate analysis		
	β	[Cl 95%]	p-value	β	[Cl 95%]	p-value
Formulation IV SC	reference	- -12,21[-13,75;-10,67]	- **<0,0001**	reference	- -10,01 [-13,22;-6,81]	- **<0,0001**
Therapy Monotherapy Combination with another IV drug	reference	-1,59 [-3,47,0,29]	0,0973	reference	-2,29 [-4,18;-0,40]	**0,0176**
Weight	0,05	[-0,01;0,10]	0,0761			
Number of pharmacy opening days/year	0,09	[-0,06;0,14]	**<0,0001**			
Number of pharmacy opening hours/week	0,34	[-0,06;0,62]	**0,0184**			
Rate of trastuzumab IV preparation*	-1,96	[-3,13;-0,80]	**0,0010**		-1,73 [-3,28;-0,19]	**0,0280**
Rate of trastuzumab SC preparation**	-0,70	[-1,55;0,15]	0,1060		-0,76[-1,53;0,01]	0,0511

**number of trastuzumab IV preparations on October 2016 / total number of chemotherapy preparations on October 2016*

*** number of trastuzumab SC preparations on October 2016 / total number of chemotherapy preparations on October 2016*

Table 3. Association between trastuzumab administration time and different factors.

	Univariate analysis adjusted on formulation			Multivariate analysis		
	β	[Cl 95%]	p-value	β	[Cl 95%]	p-value
Formulation IV SC	reference -107,30	- [-122,94;-91,66]	- **<0,0001**	reference -54,33	- [-71,83;-36,83]	- **<0,0001**
Therapy Monotherapy Combination with another IV drug	-81,61 reference	[-83,36;-49,53] -	**<0,0001** **-**	-80,17 reference	[-96,95;-63,39] -	**<0,0001** **-**
Preparation Without anticipation Partially anticipated Anticipated	reference -13,79 -65,05	- [-31,01;3,42] [-83,80;-46,30]	- 0,1161 **<0,0001**	reference -22,93 -52,95	- [-39,20;-6,66] [-71,51;-34,39]	- **0,0059** **<0,0001**
Deddated SC drcult No Yes	reference -59,67	- [-83,84;-35,49]	- **<0,0001**	reference -51,49	- [-77,71;-25,20]	- 0,0001
Medical consultation No Yes	reference 37,51	- [21,73;53,29]	- **<0,0001**	reference 33,20	- [18,33;48,07]	- **<0,0001**
Discharge mode Personal transports Sanitary transports **Nb of day hospital service opening days/year** **Nb of day hospital service opening hours/week** **Rate of trastuzumab patients*** **Rate of monotherapy SC trastuzumab**** **Rate of monotherapy IV trastuzumab***** **Rate of combination IV treatment patients****** **Deddated chair (SC clrcult)** **Dedlcated time slot (SC clrcult)**	reference 7,31 -3,98 -0,05 -0,10 -1,17 0,35 -0,15 38,66 -36,93	- [-9,03;23,65] [-30,78;22,82] [-127,64;-86,99] [-127,76;-83,18] [-4,34;2,00] [-0,23;0,91] [-1,46;1,16] [-41,72;119,05] [-82,29;8,43]	- 0,3794 0,7710 0,8638 0,7544 0,4705 0,2338 0,8195 0,3458 0,1106			

**number of patients treated by trastuzumab/number of patients treated for a breast cancer (in October 2016)*

***number of patients treated by monotherapy SC trastuzumab/number of patients treated by trastuzumab (in October 2016)*

****number of patients treated by monotherapy IV trastuzumab/number of patients treated by trastuzumab (in October 2016)*

*****number of patients treated by IV trastuzumab in combination with another IV drug/number of patients treated by trastuzumab (in October 2016)*

sessions (and patients) compared to our study. The number of observations is essential to ensure a statistical validation of the results. The number of patients included in this study respects this constraint (245 SC and 167 IV for a minimum of 135 per subgroup).

For the economic evaluation, we chose consumables cost as indicator cost because it does not depend on factors related to the organization and characteristics of the centers. This guarantees us a reliable comparison between the two formulations in this multicentric approach. Studies that also took into account the cost of hospital staff [9-11] and patient transport [14] still showed an economic gain in favor of the SC formulation.

The limitations and biases of the study are those of an observational study with real-life data collection via questionnaires. The questionnaire only describes part of the actual practice with possible information bias at time of data collecting and typing. The collected data has been grouped and recoded to avoid dispersion and make statistical analysis possible, reducing complexity and unavoidable data entry and collection errors. The questionnaire related to the organization of the centers proposed to define the existence of a dedicated SC circuit in each day hospital service with 3 modalities: dedicated chairs, dedicated time slot, another unspecified dedicated organization. After discussion with the study committee, the variability of the definition of the dedicated circuit, could lead to information bias.

A sampling plan of patients by stratification random draw could not be realized in our study because of operational constraints (technical, budget and temporal). Confounding factors between the 2 comparators groups were however managed retrospectively by adjusting the collected confounding factors. The analysis of the confounding factors notably shows the significant impact of the type of treatment (monotherapy or combination) between the two formulations. Monotherapy administration was significantly associated with formulation (IV / SC), creating a potential confounding factor. The ideal would have been to carry out the study in only one of the two groups. However, focusing only on patients treated in monotherapy or in patients treated in combination with another IV drug would not have allowed sufficient sample size. We have therefore taken this confounding factor into account in multivariate analyses.

Conclusion

This multicenter study using real-life data quantifies the benefit for patients with breast cancer overexpressing HER2 (pathway time) and for health care centers (pathway time and costs) of the administration of trastuzumab SC formulation compared to IV formulation in France.

Abbreviations

SC : subcutaneous administration; IV :intravenous administration; Pcr : complete pathological response

Competing Interests

CB is an employee of HEVA, health data company under contract with ROCHE. NB and HAR are employees of ROCHE

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