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ORIGINAL ARTICLE

Subcutaneous versus intravenous administration of trastuzumab: preference of HER2+ breast cancer patients and financial impact of its use

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Summary

Purpose: *To investigate the preference of HER2+ breast cancer patients and nursing professionals for subcutaneous (SC) versus intravenous (IV) trastuzumab and to evaluate the financial impact derived from the use of the SC formulation.*

Methods: *A cross-sectional questionnaire-based study was carried out to investigate preferences of all patients who started treatment with SC trastuzumab while they had received the IV formulation before. The preference of nursing staff in charge of preparation and administration was also analysed. The financial impact was evaluated considering the number of preparations of SC trastuzumab and the cost of IV and SC trastuzumab, the consumables used for preparation and administration and nursing staff time for preparation.*

Results: *76 female patients were included, 84% completed the questionnaire. Of the patients, 94% declared to be satisfied with the SC route and 88% would prefer SC administration if they had to choose between IV and SC. Time saving was the main reason to justify satisfaction and preference (48 and 45% respectively). The most common adverse event related to SC trastuzumab was post-injection pain in the injection site, experienced by 77% of the patients. SC trastuzumab was preferred by 100% of the nursing staff. Total annual savings using SC formulation instead of the IV were 35.332€.*

Conclusions: *SC trastuzumab is preferred by patients and the nursing staff versus the IV administration. The use of SC trastuzumab reduced the cost derived from trastuzumab administration.*

Key words: *breast cancer, cost analysis, nursing preferences, patient preferences, subcutaneous, trastuzumab*

Introduction

Breast cancer is the most common malignant neoplasia affecting women worldwide [1], accounting for the 29% of all cancers in females in Spain [2]. Between 15 to 20% of these cancers overexpress HER2 receptor, which is the therapeutic target of trastuzumab [3]. Trastuzumab was commercialised in Spain in 2000 as Herceptin®, and since then it has been administered IV requiring an initial loading bolus dose of 8mg/kg followed by 6mg/kg administered every 21 days [4]. In September 2013 a new SC formulation was authorised by the European Medicines Agency (EMA), which was made available in Spain from December 2014. This new formulation is also administered every 21 days but, as opposed to the IV administration, there is a fixed dose of 600 mg and no initial bolus is required [4].

IV trastuzumab vials contain 150 mg of a

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lyophilised formulation. For its preparation, the formulation must be reconstituted with 7.2 ml of water and subsequently the prescribed dose must be diluted in 250 ml of saline solution. This procedure can be carried out in approximately 10 min. Herceptin® SC vials contain 600 mg of trastuzumab and recombinant human hyaluronidase (rHuPH20) in a volume of 5 ml which is ready to be administered. The dose is prepared by loading the contents of the vial into a syringe via a closed system transfer device for cytotoxic drugs, which takes about 2 min. Administration times for the IV formulations are 90 min for the initial bolus and 30 min for the subsequent doses; the administration time for the SC formulation is 5 min [4].

Several studies were carried out during the development of the SC formulation of trastuzumab. Firstly, pharmacokinetic studies to establish the in vivo bioequivalence between both formulations [5-8]. These results were followed by the Hannah study, a phase III pivotal study where the non-inferiority of the SC versus the IV formulation was demonstrated allowing marketing authorisation from the EMA [9]. Thereafter, the PrefHer study was carried out, which evaluated patient preferences towards the treatments in patients under adjuvant chemotherapy treated with 4 doses of IV trastuzumab followed by 4 doses of SC trastuzumab via handheld syringe or injection device [10]. In this study, 88.9% of the patients reported preference for the SC route [11].

The medication administration route should be decided according to the following four principles: firstly, safety and efficacy and, secondly, patient preference and pharmacoeconomics. If the safety and efficacy of two injection routes are equivalent, patient preference should be considered for the reason that it could improve quality of life, experience and satisfaction related to the treatment [12]. Healthcare system costs should be also taken into account as resources are limited.

Based on the fact that two equally efficacious and safe formulations of trastuzumab are available, the aim of this study was to investigate patient satisfaction and preferences regarding SC versus IV trastuzumab and to evaluate the financial impact derived from the use of the SC formulation. Preferences of nursing staff in charge of preparation and administration of trastuzumab were also examined.

Methods

A cross-sectional study was carried out between February 2015 and February 2016. All patients who received IV trastuzumab alone or in combination with other cytotoxic drugs and started treatment with SC trastuzumab were included. Patient identification and data collection was carried out using Oncofarm® and HCIS® electronic prescribing software. Demographic variables (age, gender and weight), diagnostic variables (cancer staging grouped according to TNM Classification of Malignant Tumours system) and therapeutic variables (type of treatment: adjuvant chemotherapy, neoadjuvant chemotherapy or maintenance chemotherapy in metastatic disease) were collected.

TNM Classification of Malignant Tumours system classifies tumours according to size and extent of the primary tumour (T), number of lymph nodes with cancer (N) and the presence or absence of metastasis. The TNM combinations are grouped into five less-detailed stages: stage 0 (abnormal cells are present but have not spread to nearby tissue), stage I, II and III (cancer is present; the higher the number, the larger the cancer tumour and the more it has spread into nearby tissues) and stage IV (the cancer has spread to distant parts of the body) [13].

A questionnaire was designed to evaluate patient satisfaction and preference towards their treatments (Table 1). This questionnaire was completed when the patients came to receive their treatment at the oncology outpatient hospital, or via telephone. Two other questionnaires were designed in order to investigate nursing professional opinions and preferences for the preparation and administration of trastuzumab (Table 2). These questionnaires were completed by the nursing staff in charge of preparation and administration, respectively.

The time spent in the preparation of IV and SC doses of trastuzumab was estimated to be 10 and 2 min, respectively. This estimation was carried out by observ-

Table 1. Questionnaire to evaluate patient's opinion and satisfaction towards subcutaneous trastuzumab

Are you satisfied with the new route of administration of trastuzumab?
Yes No
Indicate the MAIN reason:
Other reasons:
Have you experienced adverse events related to the subcutaneous injection? Mark and indicate the intensity, (1=Mild/5=Severe) of those you have experienced
Post-injection pain 1 2 3 4 5
Inflammation in the injection site 1 2 3 4 5
Redness/pruritus in the injection site 1 2 3 4 5
Pain in the limb 1 2 3 4 5
None adverse events
If you had to choose between subcutaneous administration or return to the intravenous route, which route would you choose?
Intravenous Subcutaneous
Indicate the reason:

Table 2. Questionnaire to evaluate healthcare professionals' opinions and preferences for the preparation and administration of trastuzumab

Nursing staff responsible of preparation	*Nursing staff responsible of administration*
Which of the two formulations of trastuzumab, subcutaneous or intravenous, would you prefer to prepare?	Which of the two formulations of trastuzumab, subcutaneous or intravenous, would you prefer to administer?
Subcutaneous/Intravenous	Subcutaneous/Intravenous
Indicate the main reason:	Indicate the main reason:

ing the actual preparation procedure of both formulations by the staff members. The total time saved during the period of the study by preparing SC trastuzumab instead of the IV formulation was then calculated.

The annual cost derived from the use of SC trastuzumab was compared to the hypothetical cost of using the IV preparation instead, considering consumables costs used for preparation and administration of IV formulation (250 mL saline solution, water for injection and secondary set and multi-way infusion set for cytotoxic drugs) and the cost of nursing preparation time. Calculations were carried out using the wholesale acquisition cost for IV and SC trastuzumab in Spain [14], the public acquisition cost for consumable in our hospital and the cost of nursing preparation time considering the official salary of a nurse in the Spanish Public Healthcare System [15]. The patient's weight and the re-utilisation of IV trastuzumab vials for different patients were taken into account to calculate the cost of the intravenous preparations.

Statistics

Descriptive analysis was performed using Microsoft Excel 2010®. The frequency distribution and median with maximum and minimum were calculated for the qualitative and quantitative variables, respectively.

Results

A total of 76 women diagnosed with breast cancer were included in the study, whose demographic characteristics are summarised in Table 3.

Of the patients treated with SC trastuzumab, 84% completed the questionnaire. Of those who completed the questionnaire, 93.8% declared to be satisfied with the administration via the subcutaneous route, the main reasons being time saving (48.3%), convenience (28.3%) and avoiding venous access (21.7%). These and other reasons provided by the participants are listed in Table 4. Post-injection pain in the injection site was experienced by 77% of the patients, although pain intensity was considered mild in 61% of these cases. Inflammation, redness/pruritus at the injection site and pain in the limb was reported by 56, 55 and 36% of patients, respectively. No adverse events were reported by 19% of the patients (Figure 1). An 87.5% of the patients reported that they would prefer the subcutaneous route if they had to choose between IV and SC administration, time saving (44.7% of the cases) being the most common reason to justify this preference. The intrave-

Table 3. Patient demographic characteristics

Age (years)	
Median (min-max)	59 (33- 86)
Female sex, n (%)	76 (100)
Weight (kg)	
Median (min-max)	66 (44-110)
Disease stage	
Stage I, n (%)	16 (21)
Stage IIA, n (%)	22 (29)
Stage IIB, n (%)	9 (12)
Stage IIIA, n (%)	7 (9)
Stage IIIB, n (%)	10 (13)
Stage IV, n (%)	12 (16)
Chemotherapy	
Adyuvant, n (%)	63 (83)
Neoadyuvant, n (%)	1 (1)
Metastatic disease, n (%)	12 (16)

Table 4. Reasons for satisfaction or dissatisfaction with the administration of subcutaneous trastuzumab

	n	%
Patients who completed the questionnaire	64	84
Satisfied patients	60	93.8
Time saving	21	35.0
Convenience	12	20.0
No venous access	10	16.7
Time saving and convenience	5	8.3
No adverse events	4	6.7
Simple	2	3.3
Time saving and painless	2	3.3
No venous access and painless	2	3.3
No venous access and time saving	1	1.7
No reason	1	1.7
Unsatisfied patients	4	6.3
Pain	3	75.0
Fatigue	1	25.0

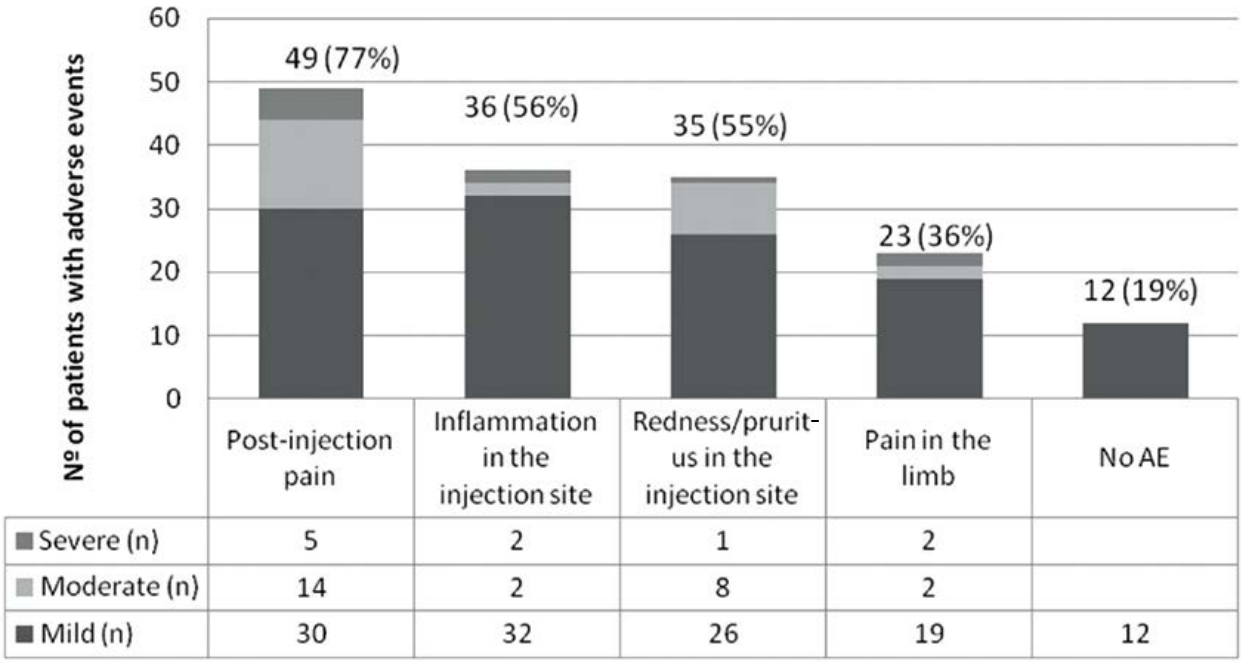

Figure 1. Adverse events (AE).

nous route was preferred by 6 patients (9.4%), of whom 3 indicated the avoidance of a double injection (one needed for analytical purposes and one for the administration of SC trastuzumab) as the main reason to justify this choice (Table 5).

SC trastuzumab was preferred to IV by 100% (n=10) of the nursing staff responsible for the preparation of oncological treatment, mainly due to preparation speed and simplicity. In addition, all of the nursing staff in charge of administration interviewed (n=13) preferred to administer trastuzumab via SC route due to time saving and convenience.

A total of 588 preparations of SC trastuzumab were manufactured during the period of the study. The total time saved by the nursing staff by preparing SC trastuzumab compared to the hypothetical time that they would have spent preparing the IV formulation was 78.4 hours.

The total cost of SC trastuzumab during the period of the study was 924.501€. In 23 of the patients the initial bolus loading dose was saved, as they started directly with the SC formulation after neoadjuvant therapy and surgery. A hypothetical use of the IV route instead of the SC route would have cost 954.091€, based on the price of trastuzumab IV per mg, a dosing regimen of 8 mg/kg for the initial bolus and 6 mg/kg for successive maintenance doses, and accounting for the re-utilisation of vials for different patients. The consumables that would have be used for a hypothetical preparation and administration of IV formulation and the hypothetical time that the nursing staff would have spent preparing the IV formulation would have cost 4.942€ and 800€, respectively. Therefore, the total annual savings were 35.332€.

Table 5. Route of administration chosen by the patients and reason for the choice

		n	%
Subcutaneous route choice		56	87.5
Reasons	Time saving	15	26.8
	No venous access	8	14.3
	Convenience	8	14.3
	Time saving and convenience	6	10.7
	No venous access and painless	3	5.4
	No venous access and time saving	3	5.4
	No adverse events	3	5.4
	Convenience and less painful	2	3.6
	Psychologically better	2	3.6
	No reason	2	3.6
	Time saving and painless	1	1.8
	Painless	1	1.8
	Simple	1	1.8
	No venous access and convenience	1	1.8
Intravenous route choice		*6*	*9.4*
Reasons	Avoidance of a double injection (clinical analysis +subcutaneous injection)	3	50.0
	Less painful	2	33.3
	Less fatigue	1	16.7
No choice		*2*	*3.1*

Discussion

In our study, of 76 women treated with SC trastuzumab 94% were satisfied with the treatment and 87.5% preferred the SC over the IV route. These results were in agreement with those of the PrefHer study, where 88.9% of the patients preferred SC trastuzumab over IV and time saving was the main reason to support this preference [10,11]. Although the results from both studies were in agreement, the patient populations included in each study differed; the PrefHer study included patients in adjuvant chemotherapy only, whereas the current study, despite a larger prevalence of patients in adjuvant chemotherapy, also included patients in neoadjuvant treatment and metastatic patients in maintenance chemotherapy. A new study called ChangHer is being carried out in the latter group of patients. This study follows a study design similar to the PrefHer but results are not yet available. Another important aspect is that in the PrefHer study SC trastuzumab was administered with handheld syringe or injection device whereas in our study the administration was performed with syringe only, as the injection device was not available. In addition to the PrefHer, another study was carried out in 7 hospitals in Germany where 70-90% of the patients preferred SC trastuzumab, also due to time saving during administration [16].

A limitation of the study was that, in addition to the cost of nursing time saved preparing the SC formulations versus the IV, the time that is also saved during administration and the reduction of patient chair time in the outpatient oncology unit was not determined. In an observational study by De Cock et al. carried out in parallel to the PrefHer study, the time saved in the preparation and administration of SC trastuzumab versus IV was investigated; the results of this study showed that the time saved per dose of SC trastuzumab was 55 min in terms of patient chair time and 17 min in preparation and administration [17]. In a study conducted in New Zealand the time saved using the SC formulation was 36.95 min in patient chair time and 20.45 min in terms of pharmacist time [18]. A similar study was conducted in the United Kingdom where the cost associated with the time spent by healthcare professionals was also considered; savings with the SC formulation accounted for £100.06 per treatment cycle [19].

There are published studies and literature reviews which support the importance of considering patient's preferences in terms of the route of administration when selecting the most suitable treatment option. These studies cover different therapeutic areas such as diabetes [20], rheumatoid arthritis [21,22], and oncology [23,24]. A study by Jin et al. suggests that understanding patient's preferences and getting the patient involved in the treatment's decisions improves patient experience, satisfaction and adherence when the patient is responsible for the administration of his own medication [12]. In the first place, treatment selection must always be performed based on the fundamental principles of safety and efficacy. However, when two formulations with different route of administration and with equivalent safety and efficacy are available, as in the case of trastuzumab, this decision should be based on efficiency and patient preferences criteria.

Currently, the SC formulation is a more efficient alternative than the IV one, both in terms of direct costs of medicines and consumables and indirect costs in terms of time spent in preparation, administration and patient chair time. Nevertheless, future studies should be carried out once biosimilar trastuzumab has reached the market, since a reduction of IV formulation cost will probably occur. As it is mentioned before efficiency is one of the criteria that must be taken into account when selecting the most appropriate treatment within a Healthcare System when different alternatives of equal efficacy and safety are available.

In conclusion, this study showed a preference of patients and nursing staff towards the SC administration of trastuzumab versus the IV route. Using SC trastuzumab provided savings considering the cost of both formulations, consumables and nursing preparation time.

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Conflict of interests

The authors declare no confict of interests.

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