Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study

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See Comment page 914

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Summary

Background Subcutaneous trastuzumab has shown non-inferior efficacy and a similar pharmacokinetic and safety profile when compared with intravenous trastuzumab in patients with HER2-positive early breast cancer. We assessed patient preference for either subcutaneous or intravenous trastuzumab in the international, randomised PrefHer study.

Methods Eligible patients were women aged 18 years or older with HER2-positive, histologically confirmed primary invasive breast adenocarcinoma, no evidence of residual, locally recurrent, or metastatic disease after completion of surgery and chemotherapy (neoadjuvant or adjuvant), an Eastern Cooperative Oncology Group performance status of 0 or 1, and a baseline left-ventricular ejection fraction of 55% or more before the first dose of trastuzumab. Radiotherapy or hormone therapy was allowed. Patients were randomised (randomly permuted blocks of four) to receive four cycles of 600 mg fixed-dose subcutaneous adjuvant trastuzumab via a single-use injection device or hand-held syringe followed by four cycles of standard intravenous trastuzumab, or the reverse sequence. Randomisation was stratified by de-novo versus non-de-novo use of intravenous trastuzumab. The primary endpoint was the proportion of patients indicating an overall preference for subcutaneous or intravenous trastuzumab, assessed by patient interview in the evaluable intention-to-treat (ITT) population (patients who completed both interviews and had at least one administration of both subcutaneous and intravenous trastuzumab). Data collection for PrefHer is ongoing. This study is registered with ClinicalTrials.gov, number NCT01401166.

Findings 124 patients were randomly allocated to receive subcutaneous followed by intravenous trastuzumab, and 124 to receive the reverse sequence. 117 patients in the subcutaneous first group and 119 in the intravenous first group were included in the evaluable ITT population. Subcutaneous trastuzumab via the single-use injection device was preferred by 216 patients (91·5%, 95% CI 87·2–94·7; p<0·0001). Only 16 patients preferred intravenous trastuzumab (6·8%, 3·9–10·8), and four had no preference (1·7%, 0·5–4·3). Clinician-reported adverse events occurred in 141 of 242 (58%) patients during the pooled subcutaneous periods and 105 of 241 (44%) patients during the pooled intravenous periods; seven (3%) and five (2%) were grade 3, no patients had a grade 4 or 5 event. The most common grade 3 adverse event was influenza (two [0·8%] patients).

Interpretation Patient preference and safety results from PrefHer, combined with the known non-inferior efficacy and pharmacokinetic and safety profile data, suggest that a fixed dose of 600 mg trastuzumab administered subcutaneously every 3 weeks is a validated, well tolerated treatment option for HER2-positive breast cancer, and is the preferred treatment of patients.

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Introduction

Treatment regimens containing trastuzumab administered intravenously are the standard of care for patients with HER2-positive breast cancer. Trastuzumab provides a significant survival benefit in early-stage disease when given as adjuvant therapy for 12 months,[1–8] and in first-line treatment of metastatic disease.[9,10]

Intravenous trastuzumab is administered according to bodyweight over 30–90 min in once-weekly or 3-weekly cycles. A subcutaneous formulation, containing a fixed dose of 600 mg trastuzumab and 10 000 U recombinant human hyaluronidase (rHuPH20, Halozyme Therapeutics, San Diego, CA, USA) as an excipient, has been developed for 3-weekly use as an alternative to the intravenous formulation. A single-use injection device provides an alternative to subcutaneous injection via hand-held syringe, and can enable self-administration.[11] Pharmacokinetic bioequivalence between the two methods of subcutaneous administration was shown in the CP3 study (NCT01344863).[11] Subcutaneous trastuzumab was well tolerated using both methods, with no grade 4 or 5, cardiac, or serious adverse events reported.[11]

The phase 3 HannaH study[12] met its coprimary endpoints of non-inferior serum trough concentration and pathological complete response with neoadjuvant or adjuvant subcutaneous trastuzumab via hand-held

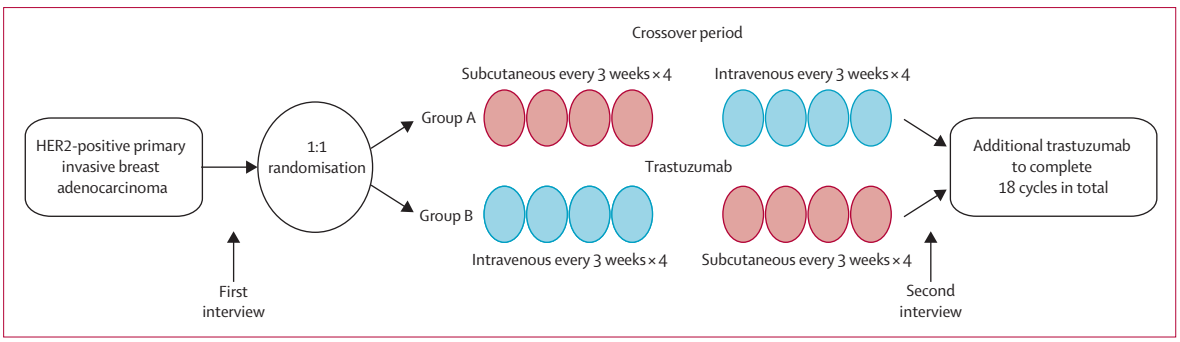

Figure 1: **Study design**

syringe versus intravenous trastuzumab in 596 patients. The overall safety profile of subcutaneous trastuzumab was consistent with the known safety profile of intravenous treatment in early breast cancer.[12] However, patient preference for route of administration has not been assessed to date.

The Preference for Herceptin SC or IV Administration (PrefHer) study was designed to assess patient preference for trastuzumab administered either subcutaneously or intravenously in the adjuvant breast cancer setting.

Methods

Study design and patients

PrefHer was an international, multicentre, open-label, randomised, two-cohort, two-arm, crossover study which used comprehensive telephone interviews to determine patient preference for route of administration of trastuzumab. The study design is shown in figure 1. Eligible patients were women aged 18 years or older with HER2-positive (immunohistochemistry 3+ or positive by in-situ hybridisation), histologically confirmed primary invasive breast adenocarcinoma, no evidence of residual, locally recurrent, or metastatic disease after completion of surgery and chemotherapy (neoadjuvant or adjuvant), an Eastern Cooperative Oncology Group performance status of 0 or 1, and a baseline left-ventricular ejection fraction (LVEF) of 55% or more before the first dose of trastuzumab. HER2-positivity was assessed using local laboratories with validated assays, according to recommendations outlined in the summary of product characteristics for intravenous trastuzumab. Radiotherapy or hormone therapy was allowed. Patients could have been either trastuzumab-naive (de-novo group) or had already received intravenous trastuzumab as part of a concurrent or sequential regimen following neoadjuvant or adjuvant chemotherapy (non-de-novo group); however, these patients must have had at least eight out of the total 18 planned 3-weekly trastuzumab cycles remaining before enrolment.

The PrefHer trial was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. Approval for the protocol was obtained from appropriate local and national independent ethics committees.

Randomisation and masking

In this open-label study, patients were randomised 1:1 using a pre-established randomisation list (prepared by S-CLINICA, Brussels, Belgium) of randomly permuted blocks of four, to receive four cycles of subcutaneous trastuzumab followed by four cycles of intravenous trastuzumab or the reverse sequence (these eight cycles are referred to as the crossover period). Randomisation was done via central interactive voice-recognition or interactive web-based response systems. Because neoadjuvant or adjuvant treatment might have also included intravenous trastuzumab, randomisation was stratified by de-novo versus non-de-novo intravenous trastuzumab. Randomisation blocks did not contain the stratification factor and were dynamically attributed to the de-novo or non-de-novo categories.

Procedures

Intravenous trastuzumab was administered every 3 weeks according to the manufacturer's label (8 mg/kg loading dose in the de-novo group, 6 mg/kg maintenance dose; around 90 min for the first loading dose infusion, 30 min for subsequent infusions).[13] Subcutaneous trastuzumab was given at a fixed dose of 600 mg/5 mL (including 10 000 U rHuPH20), injected into the thigh using the single-use injection device over roughly 5 min. A hand-held syringe cohort with a fixed dose of 600 mg given over 5 min by subcutaneous administration was added after a protocol amendment; however, this cohort will be analysed on a separate, ongoing, independent basis, and the results will be reported elsewhere when complete. If intravenous trastuzumab was delayed for more than 7 days, a reloading 8 mg/kg dose was administered. Dose reductions were not permitted. After the crossover period, patients continued intravenous or subcutaneous trastuzumab to complete a total of 18 treatment cycles (amended from the initially planned 22 once subcutaneous non-inferiority[12] was shown). All patients received subcutaneous or intravenous trastuzumab from a health-care professional in the clinic, there was no self-administration in the crossover period.

The primary endpoint of this study was the proportion of patients indicating an overall preference for either

the subcutaneous or intravenous route of administration. Assessment of factors affecting patient preference was an exploratory endpoint (specified in the protocol), as were analyses of strength of preferences and reasons for them. Secondary endpoints included safety and tolerability, event-free survival (time to local, regional, or distant recurrence, contralateral breast cancer, or death from any cause), immunogenicity (anti-trastuzumab and anti-rHuPH20 antibodies in blood samples; single-use injection device cohort only), satisfaction of the health- care professional, and perceived time savings with subcutaneous trastuzumab administration. A time-and-motion pharmacoeconomic substudy is assessing the use of medical care, including collection of time of administration and resource use data.[14–16]

Patients' preferences for route of administration, the strength of their preferences, other influencing factors, and reasons for them were elicited from two study-specific telephone interviews (full interview text can be found in the appendix). Factors potentially affecting preferences were also examined through logistic regression. The first interview was done at baseline, before randomisation, lasted around 15 min, and consisted of 37 questions that assessed issues such as previous experiences with different types of drug delivery and with chemotherapy administration, and expected preferences for subcutaneous or intravenous administration of trastuzumab. The second interview was done after the crossover period had been completed, lasted around 25 min, and consisted of 61 questions eliciting information about venous access type or issues, experiences with the single-use injection device, travelling time to the cancer centre, and relationship with the health-care professionals. The two main reasons for the patients' final preferences were recorded verbatim, together with the strength of preferences.

See Online for appendix

Since no standardised instruments were available, these study-specific interview schedules were done with the use of a standardised iterative methodology. Initially, to establish face validity, experienced clinicians, chemotherapy nurses, and psychologists generated a list of topics that might affect preferences, such as needle phobias, previous experiences during intravenous chemotherapy administration, and relationship with staff at the chemotherapy centre. These topics were then formulated into questions and discussed again for relevance and intelligibility before ordering as an interview schedule and piloting. After several modifications, the interviews were tested with patient volunteers from patient advocacy groups including Independent Cancer Patients' Voice, all of whom had previously received treatment for breast cancer. Based on this feedback, further modifications were made to improve clarity and remove ambiguities before re-testing. When all parties were confident that the interviews had both face and content validity, this version was translated and back-translated into Danish, French, German, Italian, Polish, Russian, Spanish, and Swedish for field testing in 11 participating countries in the single-use injection device cohort. Remaining irregularities or confusions caused by translation were corrected.

All interviewers were native speakers of the relevant languages, were independent of the treating centre, and had in-depth training, which included a comprehensive manual with photographs and descriptions of the different methods of administering intravenous drugs. No interviewer was permitted to undertake any study interviews until satisfactory completion of training and practice interviews and quality control with regular checks ensured that interviewers were not leading the patients. Interviewers did not have knowledge of the protocol or hypotheses. Data input was done online, and interviewers translated any free text verbatim and created hard copies for checking in parallel. An independent native speaker also checked the interviews contemporaneously to ensure impartial questioning.

Health-care professional satisfaction and perceived time savings were assessed by a questionnaire (HCPQ, appendix). Safety was assessed by physical examination and vital signs every 3 months. Cardiac function was monitored by echocardiogram or multi-gated acquisition scan every four cycles of trastuzumab and at 6, 12, and 24 months after cessation of treatment, or according to institutional practice. Adverse events, symptomatic LVEF, and serious adverse events were graded and reported according to standard National Cancer Institute–Common Terminology Criteria for Adverse Events V4.0,[17] New York Heart Association,[18] and International Conference on Harmonisation E2A[19] guidelines. Patients will be followed up until 3 years after the last randomisation, or until disease recurrence (whichever occurs first).

Statistical analysis

Analyses of patient preferences were done on the evaluable intention-to-treat (ITT) population (patients who received at least one dose of trastuzumab by both subcutaneous and intravenous administration and completed the first interview and the primary endpoint question in the second interview) after crossover. The proportion of patients preferring subcutaneous trastuzumab and the 95% CIs (exact binomial method) were calculated. For the sample size calculation, we assumed that 65% of patients would prefer subcutaneous trastuzumab. The margin of error within which the estimated proportion is given was chosen to be 7·5%; therefore, a sample size of 160 patients was needed for the 95% CIs to be within 57·5% and 72·5%. 200 patients per cohort were needed to allow for 20% of patients not providing an evaluable preference assessment (calculated by nQuery Advisor Version 6).

Statistical preference for subcutaneous administration was compared in a non-protocol-specified analysis with

a two-sided test against the null hypothesis value of 65%. The potentially influencing factors: study group (single-use injection device followed by intravenous administration group *vs* intravenous followed by single-use injection device group), pre-study trastuzumab treatment, country, age (<60 *vs* ≥60 years), weight (<80 *vs* ≥80 kg), expected preferences given in the first interview (subcutaneous *vs* intravenous or no preference), needle phobia or anxiety (yes *vs* no), difficulty to travel to chemotherapy appointments (yes *vs* no), and intravenous delivery type (cannula *vs* venous access device or both; as assessed at both the first and second interviews) were assessed in terms of their effect on the primary endpoint using logistic regression (forward selection by stepwise regression with alpha 0·05) in an exploratory manner. Medical histories and concomitant medications were collected at screening and recorded throughout but were not considered for this analysis because of the diversity of drugs and conditions. Statistical analyses were done with SAS (version 9.1.3).

The safety population comprised all patients who received at least one dose of study treatment. Adverse event data are descriptive only.

This study is registered with ClinicalTrials.gov, identifier NCT01401166.

Role of the funding source

The sponsor was involved in study design and data interpretation. Employees of the sponsor gathered and managed data, and undertook statistical analyses. Patient interviews were administered and data collected independently of the sponsor by SHORE-C. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

From Oct 27, 2011, to March 29, 2012, 265 patients completed the first interview, and 248 patients were randomised (figure 2) at 56 centres in Europe and Canada. Four randomised patients did not receive study treatment, so the safety population consisted of 244 patients: 122 per study group. Ten patients who were treated did not complete all eight cycles of trastuzumab, owing to disease recurrence (four), adverse events (three), withdrawal of consent (one), loss to follow-up (one), and refusal of treatment (one). Of these ten patients, two did nevertheless receive both routes of administration and completed the primary endpoint question in the second interview; therefore, they were included in the evaluable ITT population. The remaining eight patients did not complete the primary endpoint question in the second interview; therefore, the evaluable ITT population consisted of 236 patients: 117 patients who received subcutaneous trastuzumab followed by intravenous trastuzumab, and 119 patients who received intravenous and then subcutaneous trastuzumab. No data were missing, since all evaluable ITT patients completed both interviews.

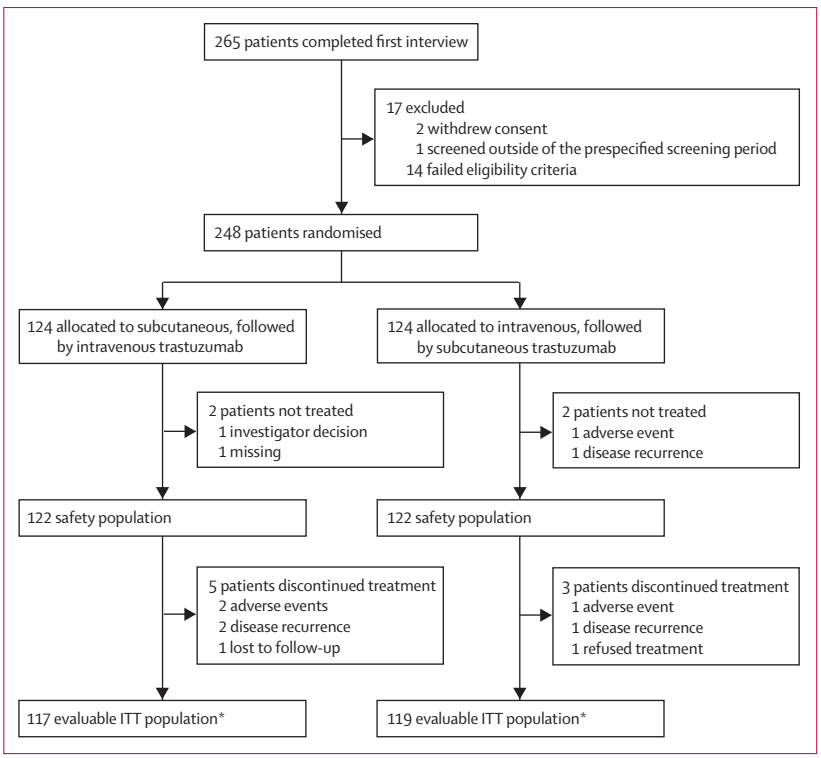

***Figure 2*: Trial profile**

*Patients who received at least one dose of trastuzumab via subcutaneous and intravenous administration and completed the baseline interview and the primary endpoint question in the second interview. Subcutaneous trastuzumab was administered by single-use injection device in all cases.

Baseline patient demographics, tumour characteristics, and treatment history were generally balanced between study groups (table 1). The median age of all patients was 53·0 years (IQR 45·0–62·0) and the median weight was 68·0 kg (61·0–79·0). 163 patients were younger than 60 years and 73 were 60 years or older. Most patients had previously received trastuzumab. At the time of data cutoff (Sept 19, 2012), two patients received more than 18 cycles of trastuzumab, since they were treated before the protocol was amended from 22 to 18 cycles.

At the second interview, 216 of 236 (91·5%) patients preferred subcutaneous trastuzumab (95% CI 87·2–94·7; p<0·0001), 16 (6·8%, 3·9–10·8) preferred intravenous administration, and four (1·7%, 0·5–4·3) had no preference.

In the patients who had received subcutaneous trastuzumab first, 112 of 117 (95·7%) preferred subcutaneous administration (95% CI 90·3–98·6), and five of 117 (4·3%, 1·4–9·7) preferred intravenous administration. No patients answered "no preference". In the patients who received intravenous trastuzumab first, 104 of 119 (87·4%, 80·1–92·8) preferred subcutaneous administration, 11 of 119 (9·2%, 4·7–15·9) preferred

	Subcutaneous followed by intravenous trastuzumab group (n=117)	Intravenous followed by subcutaneous trastuzumab group (n=119)
Age, years	55·0 (48·0–63·0)	51·0 (42·0–62·0)
Weight, kg	69·0 (62·4–80·0)	65·7 (60·7–76·0)
ECOG at screening		
0	95 (81%)	96 (81%)
1	22 (19%)	23 (19%)
TNM classification at diagnosis		
Primary tumour*		
T0	2 (2%)	4 (3%)
T1	60 (51%)	39 (33%)
T2	38 (32%)	57 (48%)
T3	9 (8%)	11 (9%)
T4	6 (5%)	8 (7%)
Unknown	2 (2%)	0
Lymph node status		
Negative	63 (54%)	51 (43%)
Positive	48 (41%)	66 (55%)
Unknown	6 (5%)	2 (2%)
HER2-positive		
Yes	117 (100%)	119 (100%)
No	0	0
Stratification factor: adjuvant trastuzumab		
De-novo	29 (25%)	28 (24%)
Non-de-novo	88 (75%)	91 (76%)
Previous treatment		
Chemotherapy	117 (100%)	119 (100%)
Radiotherapy	72 (62%)	71 (60%)
Hormonal therapy	50 (43%)	50 (40%)
Lapatinib	0	1 (1%)

Data are median (IQR) or number (%). All patients received prior surgery. ECOG=Eastern Cooperative Oncology Group. *No tumours were metastatic. All patients received neoadjuvant or adjuvant chemotherapy, or both.

Table 1: **Patient demographics, tumour characteristics, and treatment history (evaluable intention-to-treat population)**

	n*
Subcutaneous preferred, n=216	
Time saving	195
Less pain/discomfort	88
Convenience to patient	35
Ease of administration	33
Problems with intravenous	25
Less stress/anxiety	15
Other	6
Intravenous preferred, n=16	
Fewer reactions (less pain, bruising, irritation, etc)	11
Other	5
Environment/staff	2
Perceived efficacy	1
Ecological considerations	1

Responses to the question "What are the two main reasons for your preference?" were recorded verbatim by the interviewer. Four experienced researchers independently scrutinised the dataset and provided over-arching themes or core categories for coding. When broad consensus about these had been reached each researcher independently coded every patient's response; the researchers then reconciled codings with each other and determined if any thematic categories could reasonably be collapsed together or if a new category was required.*Some patients gave more than one reason for preference.

Table 2: **Primary reasons for patients' preferences (evaluable intention-to-treat population)**

intravenous administration, whereas four of 119 (3·4%, 0·9–8·4) had no preference.

The preference for subcutaneous trastuzumab was seen irrespective of trastuzumab therapy before enrolment (54 of 57 [94·7%, 85·4–98·9] in the de novo group and 162 of 179 [90·5%, 85·2–94·4] in the non-de-novo group).

Two terms were found to be significant and therefore kept in the final stepwise logistic regression model to select factors that potentially influence preference: study group (odds ratio [OR] 3·28, 95% CI 1·14–9·48) and venous access type (4·61, 1·48–14·37). However, these results should be interpreted with caution due to the low number of patients who either expressed a preference for intravenous or did not express a preference in one of the subgroups. Preference for subcutaneous trastuzumab was 94·6% (95% CI 89·1–97·8) for patients receiving intravenous trastuzumab by cannula (122 of 129 patients) and 87·4% (79·4–93·1) for those with a venous access device (90 of 103 patients). As with the primary analysis, trastuzumab therapy before enrolment did not affect preference. Hypothetical preference, as assessed in the first interview, for subcutaneous trastuzumab was 45·8% (108 of 236 patients) before randomisation (appendix) and also did not affect final preference. Patients also preferred subcutaneous trastuzumab irrespective of their country (appendix).

Overall preference for subcutaneous trastuzumab was "very strong" in 159 of 236 patients (67·4%, 95% CI 61·0–73·3), "fairly strong" in 45 (19·1%, 14·3–24·7), and "not very strong" in 12 (5·1%, 2·7–8·7). Overall preference for intravenous trastuzumab was "very strong" in eight (3·4%, 1·5–6·6) patients, "fairly strong" in three (1·3%, 0·3–3·7), and "not very strong" in five (2·1%, 0·7–4·9).

The two main reasons patients gave for preferring subcutaneous administration were that it either saved time or resulted in less pain and discomfort (table 2). Patients reported that the single-use injection device was less painful than intravenous administration (158 of 236 patients [66·9%] *vs* 33 [14·0%]; 45 of 236 [19·1%] reported no difference); it also caused less bother from bruising (109 [46·2%] *vs* 33 [14·0%]; 94 [39·8%] reported no difference) or from irritation to the injection site (84 [35·6%] *vs* 35 [14·8%]; 117 [49·6%] reported no difference).

103 health-care professionals completed the questionnaire about their preferences. Most were more satisfied with the subcutaneous administration of trastuzumab (76 [73·8%], 95% CI 64·2–82·0) than the intravenous administration (two of 103 [1·9%], 0·2–6·8). The remaining 25 (24·3%, 16·4–33·7) expressed no preference for either route of administration. Data for satisfaction of health-care professionals by country were not assessed, and patients' body-mass index was not considered.

	Subcutaneous administration period (both groups pooled, n=242)	Intravenous administration period (both groups pooled, n=241)	Crossover period (both groups pooled, n=244)
Adverse events (all NCI-CTCAE grades)	141 (58%)	105 (44%)	164 (67%)
Grade 1 (mild)	124 (51%)	78 (32%)	148 (61%)
Grade 2 (moderate)	53 (22%)	46 (19%)	78 (32%)
Grade 3 (severe)	7 (3%)	5 (2%)	11 (5%)
Grade 4 (life-threatening)	0	0	0
Grade 5 (death)	0	0	0
Most frequent adverse events (≥5% of patients, all NCI-CTCAE grades)			
Arthralgia	9 (4%)	15 (6%)	21 (9%)
Grade 1 (mild)	8 (3%)	12 (5%)	17 (7%)
Grade 2 (moderate)	1 (<0·5%)	3 (1%)	4 (2%)
Grade 3 (severe)	0	0	0
Injection site reaction (preferred term)*	19 (8%)*	0	19 (8%)*
Grade 1 (mild)	18 (7%)	0	18 (7%)
Grade 2 (moderate)	2 (1%)	0	2 (1%)
Grade 3 (severe)	0	0	0
Asthenia	12 (5%)	7 (3%)	18 (7%)
Grade 1 (mild)	6 (3%)	3 (1%)	8 (3%)
Grade 2 (moderate)	6 (3%)	3 (1%)	9 (4%)
Grade 3 (severe)	0	0	0
Missing	0	1 (<0·5%)	1 (<0·5%)
Nausea	14 (6%)	5 (2%)	17 (7%)
Grade 1 (mild)	10 (4%)	5 (2%)	13 (5%)
Grade 2 (moderate)	3 (1%)	0	3 (1%)
Grade 3 (severe)	0	0	0
Missing	1 (<0·5%)	0	1 (<0·5%)
Fatigue†	8 (3%)	8 (3%)†	16 (7%)†
Grade 1 (mild)	7 (3%)	6 (3%)	13 (5%)
Grade 2 (moderate)	1 (<0·5%)	2 (1%)	3 (1%)
Grade 3 (severe)	0	1 (<0·5%)	1 (<0·5%)
Cardiac adverse events‡	6 (3%)	3 (1%)	9 (4%)
Ejection fraction decreased	3 (1%)	0	3 (1%)
Grade 1 (mild)	3 (1%)	0	3 (1%)
Grade 2 (moderate)	0	0	0
Left ventricular dysfunction	2 (1%)	1 (<0·5%)	3 (1%)
Grade 1 (mild)	1 (<0·5%)	0	1 (<0·5%)
Grade 2 (moderate)	1 (<0·5%)	1 (<0·5%)	2 (1%)
Bradycardia	0	1 (<0·5%)	1 (<0·5%)
Grade 1 (mild)	0	0	0
Grade 2 (moderate)	0	1 (<0·5%)	1 (<0·5%)
Palpitations	1 (<0·5%)	0	1 (<0·5%)
Grade 1 (mild)	1 (<0·5%)	0	1 (<0·5%)
Grade 2 (moderate)	0	0	0
Heart valve incompetence	0	1 (<0·5%)	1 (<0·5%)
Grade 1 (mild)	0	1 (<0·5%)	1 (<0·5%)
Grade 2 (moderate)	0	0	0

(Continues on next page)

	Subcutaneous administration period (both groups pooled, n=242)	Intravenous administration period (both groups pooled, n=241)	Crossover period (both groups pooled, n=244)
(Continued from previous page)			
Injection site reactions (pooled term, all NCI-CTCAE grades)‡	47 (19%)	0	47 (19%)
Administration-related reactions (all NCI-CTCAE grades)‡	22 (9%)	11 (5%)	33 (14%)
Serious adverse events (ICH E2A)	4 (2%)	2 (1%)	6 (3%)
Related to study treatment	0	0	0
Fully resolved without sequelae	4 (2%)	2 (1%)	6 (3%)
Study drug discontinued because of adverse events	2 (1%)	1 (<0·5%)	3 (1%)

Data are number (%). ICH=International Conference on Harmonisation. NCI-CTCAE=National Cancer Institute–Common Terminology Criteria for Adverse Events. *One patient had both grade 1 (mild) and grade 2 (moderate) injection site reactions and so is counted once in each NCI-CTCAE grade and once overall. †One patient had both grade 2 (moderate) and grade 3 (severe) fatigue and so is counted once in each NCI-CTCAE grade and once overall. ‡All were reported at grade 1 (mild) or 2 (moderate). If a patient had multiple events of the same NCI-CTCAE grade or relationship category, they were counted only once in that NCI-CTCAE grade or relationship category. Patients could be counted in both the single-use injection device and intravenous period columns, and only once in the cross-over period column.

Table 3: **Adverse event profile during the cross-over period (four cycles of subcutaneous trastuzumab and four cycles of intravenous trastuzumab, safety population)**

The adverse event profile obtained during the crossover period at the interim analysis is shown in table 3. During the pooled subcutaneous and intravenous periods, 164 of 244 (67·2%) patients experienced at least one adverse event, and most were grade 1 (148 [60·7%]) or grade 2 (78 [32·0%]). Grade 3 events were reported in 11 (4·5%) patients, and no patients had a grade 4 or 5 adverse event. Arthralgia (21 [8·6%] patients), and localised injection site reactions (19 [7·8%] patients) were the most common events overall, with influenza being the most common grade 3 adverse event (two [0·8%] patients). Differences between rates in the pooled subcutaneous and intravenous periods were driven by grade 1 events occurring more frequently during the subcutaneous period. The main driver of differences in grade 1 events was localised reactions in the injection site. All injection site reactions and systemic administration-related reactions were grade 1 or 2. Serious adverse events were reported in six of 244 patients (2·5%, events reported: mental crisis, axilla abscess, expander infection, and haematoma during the subcutaneous period, and influenza and fibroadenoma during the intravenous period), none of which were considered to be related to trastuzumab and each was resolved completely. Study drug discontinuations due to adverse events occurred in two (0·8%) patients during the subcutaneous period and one (0·4%) patient during the intravenous period. All reported cardiac events were grade 1 or 2 and none were serious. Ejection fraction decreases or left-ventricular dysfunctions were reported in five (2·1%) of 236 patients during the subcutaneous period and one (0·4%) during the intravenous period. All were considered to be related to the study drug and all were fully resolved except one of case grade 2 left-ventricular dysfunction, which was ongoing at the time of analysis.

Discussion

PrefHer showed that patients preferred fixed-dose subcutaneous delivery of trastuzumab via a single-use injection device over standard intravenous administration for the treatment of HER2-positive early breast cancer (panel).

Confirmed advantages of subcutaneous trastuzumab administration include improved patient convenience (injection time less than 5 min *vs* 30–90 min for intravenous administration,[13] which is important in long-term or single-agent trastuzumab therapy) and reduced use of hospital resources and the time of health-care professionals.[14–16,20,21] Drugs with fixed doses also have the advantages of improved compliance and ease of preparation, and reduced probability of dosing errors;[22] however, no studies to date have examined patient preference for route of trastuzumab administration. In PrefHer, the most common reason for preference of subcutaneous trastuzumab administration by patients was time saving. Actual recorded patient time savings were shown in the time-and-motion substudy, where time spent in infusion chairs with single-use injection device versus intravenous was reduced by 68% to 80% per country,[16] confirming the convenience advantage of subcutaneous trastuzumab to patients. Likewise the time-and-motion substudy showed that health-care professionals were more satisfied with the subcutaneous single-use injection device administration of trastuzumab in PrefHer, and it reduced administration time.[16]

The safety profile of four cycles of subcutaneous trastuzumab and four cycles of intravenous trastuzumab seen during the crossover period was consistent with the known safety profile of trastuzumab administered intravenously in early breast cancer.[13] Ongoing review of safety data has not raised any concerns so far. Although clinician-reported adverse events were increased with subcutaneous administration in PrefHer, this pattern was not seen in patient-reported events, where reduced pain or discomfort was the second most common reason for preference of subcutaneous administration. This discrepancy[23,24] will be assessed in future exploratory

analyses. The safety analyses reported here were limited by the point at which data were obtained (during the crossover period), by the sample size, and also by the fact that patients received trastuzumab both subcutaneously and intravenously, making assessment of the subcutaneous-specific safety profile over the full observation period difficult. Since safety data were obtained during trastuzumab monotherapy in PrefHer, a direct comparison with the HannaH study[12] cannot be made (concomitant chemotherapy was given in HannaH, which could have affected the adverse event profile). Drug exposures and observation times also differed between the two studies.

The prospective, international, open-label, non-randomised, two-cohort SafeHer study (NCT01566721) is ongoing at over 400 sites and will assess the safety and tolerability of adjuvant subcutaneous trastuzumab (via hand-held syringe injection and assisted or self-administered single-use injection device in separate cohorts), with or without chemotherapy, in 2500 patients with HER2-positive early breast cancer,[25] with a follow-up period of 5 years to allow long-term safety assessments.

The main strengths of PrefHer lie with its prospective randomised design and the primary analysis. Patients were asked their preference by an independent interviewer in a comprehensive, quality-controlled interview process, which we believe is the optimum and most convenient way to establish patient preference. This method contrasts with commonly used assessments, including retrospective assessments, questionnaires completed by the treating institution, or health-care professional-based preference reporting. Interviewers were independent of the study team and were trained to ensure that they did not lead patients or press them too hard for preferences; this approach is confirmed by the fact that the overall preference for subcutaneous trastuzumab was "very strong" or "fairly strong" in most cases. Had interviewers pressed patients to provide preferences, then these responses would have been less strong. The study design was original in this setting, and included a crossover period which allowed patients to experience both methods of administration. The validity of this approach is highlighted by the results that expected preferences, as assessed by the first interview, were lower than actual preferences after experiencing both methods. The only two factors that seemed to affect patient preference in an exploratory logistic regression analysis were type of venous access and administration sequence. No other factors had an effect on preference, which reinforces the primary results.

In conclusion, patient preference and safety results from PrefHer, combined with efficacy, pharmacokinetic, and safety results from HannaH, suggest that a fixed dose of 600 mg subcutaneous trastuzumab every 3 weeks is a validated, well tolerated, and preferred option of patients for the treatment of HER2-positive breast cancer.

Panel: Research in context

Systematic review

Trastuzumab is currently administered intravenously according to bodyweight. Addition of recombinant human hyaluronidase (rHuPH20) allowed development of a fixed-dose subcutaneous formulation. The phase 3 HannaH study showed non-inferior efficacy and a similar pharmacokinetic and safety profile between the subcutaneous and intravenous formulations of trastuzumab.[12] A subcutaneous single-use injection device is under development and shows bioequivalence to subcutaneous administration via hand-held syringe.[11] Patient preference for subcutaneous or intravenous administration of trastuzumab has not been taken into account to date.

Interpretation

Patient preference and safety results from PrefHer, combined with efficacy, pharmacokinetic, and safety results from HannaH, suggest that a fixed dose of 600 mg subcutaneous trastuzumab every 3 weeks is a validated, well tolerated treatment option for HER2-positive breast cancer and is preferred by patients.

Event-free survival from PrefHer will be reported when appropriate follow-up has occurred and immunogenicity endpoints will be reported elsewhere. Data collection for PrefHer is ongoing at over 70 sites in 12 countries across both the single-injection device cohort and the hand-held syringe cohort, which completed enrolment on Dec 3, 2012, with 240 patients from ten countries.

Contributors

All authors reviewed the data analyses, contributed to the writing of the report, made final decisions on all parts of the report, and approved the final version of the submitted report. XP and LF participated in study design. LJ and VJ were responsible for development and testing of the patient interviews, overseeing translations, and field testing and training of interviewers. XP, JG, VM, SV, AK, VS, and GL-V enrolled patients. SO undertook statistical analyses. LF, VJ, SO, and NS contributed to data collation and generation of tables and figures. The academic authors vouch for the completeness and veracity of the data and data analyses.

Conflicts of interest

XP has received honoraria from F Hoffmann-La Roche, GlaxoSmithKline, and TEVA. JG has received honoraria for consultancies and speakers' bureaux from F Hoffmann-La Roche, and has received travel grants from F Hoffmann-La Roche. PB-L has acted on advisory boards for and received honoraria from Roche Products. VM has received speaker honoraria from Amgen, Celgene, Sanofi-Aventis, Pierre-Fabre, and F Hoffmann-La Roche, and research funding from F Hoffmann-La Roche. SV has consulted for, received honoraria from, and participated in advisory boards for F Hoffmann-La Roche. VJ and LF received research funding from F Hoffmann-La Roche to undertake and coordinate the patient interviews for the study. NS is an employee of and holds stocks in F Hoffmann-La Roche. SO is an employee of F Hoffmann-La Roche. AK, GC, VS, and GL-V declare that they have no conflicts of interest.

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