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Implications of subcutaneous or intravenous delivery of trastuzumab; further insight from patient interviews in the PrefHer study

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Abstract

Background

The 2 Cohort randomised PrefHer trial examined the preferences of HER2+ primary breast cancer patients for intravenous (IV) or subcutaneous (SC) delivery of trastuzumab via a Single Injectable Device (SID) or hand-held syringe (HHS). The novel approach and design of the study permitted an in-depth exploration of patients' experiences, the impact that different modes of delivery had on patients' well-being and implications for future management.

Methods

The preferences, experiences and general comments of patients in the PrefHer study were collected via specific semi-structured interview schedules. Exploratory analyses of data were conducted using standard methodology. The final question invited patients to make further comments, which were divided into 9 thematic categories – future delivery, compliments, time/convenience, practical considerations, pain/discomfort, study design, side-effects, psychological impact, and perceived efficacy.

Results

267/467 (57%) patients made 396 additional comments, 7 were neutral, 305 positive and 86 negative. The three top categories generating the largest number of comments were compliments and gratitude about staff and being part of PrefHer (75/396; 19%), the potential future delivery of SC trastuzumab (73/396; 18%), and practical considerations about SC administration (60/396;15%).

Conclusions

Eliciting patient preferences about routes of administration of drugs via comprehensive interviews within a randomised cross-over trial yielded rich and important information. The few negative comments made demonstrated a need for proper staff training in SC administration Patients were grateful to have been part of the trial, and would have liked to continue with SC delivery. The possibility of home administration in the future also seemed acceptable.

Keywords

Patient preferences, drug administration, trastuzumab, breast cancer

Introduction

There has been increasing recognition that inclusion of patient reported outcome (PRO) data enables better opportunities for more informed decision-making. For example standardised quality of life (QoL) instruments offer a broader assessment of the impact that different treatments exert on patients' physical, functional, emotional and social well-being compared with adverse event reporting by physicians [1]. Other types of PROs such as patient preferences using study specific interview schedules may refine and influence decision-making further, but few trials conducted to date have such measures as their primary outcome [2].

Anti-cancer drugs can be given orally, parentally, intravenously (IV) and subcutaneously (SC). All modes of administration have clinical and practical advantages and disadvantages; several of these may also have considerable impact upon patients' QoL including convenience, pain and discomfort. Treatment can demand frequent or lengthy hospital visits, and issues such as the disruption to social, occupational, or family responsibilities are frequently over-looked. Out of pocket expenses for travel and time off work incurred by patients and their families are rarely considered. If drugs or methods for administering them have similar efficacy, then patient preferences could be important, but such information is rarely captured in trials. Health economics studies employing discrete choice and time trade-off methods do determine hypothetical preferences, but data from these do not necessarily help individual patients and doctors with decision-making. Few preference studies have been conducted within oncology contemporaneously, in real time with patients making choices between administration methods that they have actually experienced. If the safety and efficacy of different administration routes are equivalent, then the most important factor should be patient preference to ensure optimal treatment adherence and ultimately improve patients' experiences and satisfaction with treatment [3].

Trastuzumab has revolutionised the treatment of HER2+ve breast cancer improving overall survival [4, 5]. However, women with HER2+ve early breast cancer need hospital based treatment lasting months or years. Most patients require surgery, adjuvant chemotherapy (usually given intravenously for 4-6 months) and/or hormone therapy and radiotherapy (often given daily for 4-6 weeks), as well as trastuzumab. Adjuvant trastuzumab is given IV every week or every 3 weeks for a total of 1 year. For many patients this is a considerable burden and disrupts their attempts to resume a more normal life-style. The Hannah trial [6] showed that a fixed dose SC formulation of trastuzumab administered using a hand-held syringe (HHS) was non-inferior to trastuzumab administered by IV as far as pCR and serum trough were concerned and no new safety signals were identified. These data formed the basis of approval by the EMA for the SC formulation in HER2+ve early and metastatic breast cancer. The SC formulation in HannaH was given via a hand-held syringe (HHS) but it can also be administered via a Single Injectable Device (SID).

The international, open-label, randomised PrefHer study (NCT01401166) examined preferences of patients with HER2+ve primary breast cancer for either IV or SC delivery of trastuzumab. The prospective, cross-over design addressed many of the limitations of previous work and unusually had patient preference as the primary outcome [2]. The trial was conducted in 10 European countries, in Turkey and Canada. In Cohort 1, 236 patients had their trastuzumab administered via a SID and in Cohort 2, 231 patients had SC delivery via a HHS. Results for both Cohorts 1 and 2 showed an overwhelming and strong preference for the SC route of administration [7, 8]. The primary reasons for those (415/467; 89%) who preferred SC were that it saved time and resulted in less pain and discomfort. Among the small number of patients (45/467; 10%) who preferred IV trastuzumab, fewer bothersome reactions including less pain, bruising, and irritation were the primary reasons given [7, 8]. We report here a more in depth

exploratory analysis of patients' experiences with IV and SC administration of trastuzumab, and the implications that these may have for staff training and future management.

Methods

Procedure

The study design has been reported previously [8]. Briefly after completion of (neo) adjuvant chemotherapy, consenting patients with HER2+ve early breast cancer were randomised to receive either 4 cycles of SC trastuzumab (600mgs fixed dose) via the SID (Cohort 1) followed by 4 cycles of standard IV or the reverse sequence and in Cohort 2, the design was identical but trastuzumab was given SC via a HHS. Prior to randomisation and also at the end of the cross-over period, patients were interviewed by phone at home, at a convenient time of their own choosing by experienced, independent interviewers.

Assessments

Study-specific Patient Interview Schedules (PINTs) were developed using an iterative procedure with the assistance of chemotherapy nurses, oncologists, psycho-oncologists and patients. After careful piloting and testing with English & French patient volunteers, further modifications were made and interviews translated before field testing in the 10 relevant languages for the 12 countries participating in the study (Canada, Denmark, France, Germany, Italy, Poland, Russia, Spain, Sweden, Switzerland, Turkey and UK).

The first PINT interview questions explored needle phobia/anxieties, past encounters with subcutaneous injections (e.g. vaccinations or heparin), previous experiences with IV chemotherapy administration via a cannula, PICC or port-a-cath, any difficulties with these such as pain, bruising or infection, and finally issues concerned with the setting where treatment was

received including relationship with staff at the chemotherapy centre and time and cost of travel there.

The primary outcome explored in the second interview, conducted after the cross-over period when patients had experienced both IV and SC routes of administration, was preference for route of administration and primary reasons contributing to these. PINT2 revisited some of the PINT 1 questions and also addressed new topics, one of which was the hypothetical preferences for place where treatment should be administered, e.g. at home, in primary care, a local hospital or the cancer centre. In addition, women were encouraged to elaborate on any other issues associated with trastuzumab administration in the trial.

Interviewers

All interviewers from a medical interviewing organisation underwent study specific training on how to conduct the PrefHer interviews. They were also given a comprehensive training manual with a frequently asked questions section, to help them understand the types of venous access devices used for IV trastuzumab administration. All had to complete interviews with simulated patients before being approved to conduct them with study patients. Interviewers adhered to comprehensive standard operating procedures and entered data on-line. Contemporaneous quality control was conducted to ensure completion of PINTs, and avoidance of missing data.

Interviews for Cohort 1 using the SID ran from Oct 2011 to mid-September 2012, and those for Cohort 2 using HHS between April 2012 and June 2013.

Analyses

The analyses in this paper focus on patients' experience of receiving trastuzumab, including assessment of the environment, delivery time and the further comments made by participants

about the different treatment administration methods (question 61 the final question of the PINT2).

The free responses from the final question (Q61) were recorded verbatim by the interviewer. Two experienced researchers using standardized methods, initially reviewed the responses given to generate thematic categories for initial coding and division. Redundant categories were removed and/or new ones created before establishing a 'code-book' of 9 categories. Four raters (VAJ, LJF, KM, CL) then independently coded the comments into 9 thematic categories.After independent coding any discrepancies were reconciled as needed. The 391 responses that participants gave to Q61 were most often one or two words or a phrase, and therefore easy to categorise. As such there was very little variation (95% agreement) between the coders The few discrepancies were all discussed and reconciled. For the final analyses, raters thoroughly reviewed the comments again within the categories to determine if they were positive, neutral or negative,

All coders were part of the main PrefHer study team, two of whom (LJF and VAJ) had had a major role in developing and testing the PrefHer semi-structured interview schedules, and in training the foreign language interviewers.

Results

Both PINTs were completed by 467 randomised patients (236 for Cohort 1 and 231 for Cohort 2). Baseline patient demographics, tumor characteristics, and treatment history were balanced between study arms [8]. Most patients (373/467; 80%) had already been receiving IV trastuzumab.

Experience of receiving trastuzumab

The majority of patients (376/467; 81%) received trastuzumab in the hospital, which for most (75%) was also the same department where they previously had chemotherapy. Travelling to receive treatment was not a problem overall (414/467; 89%) with only 6% (27/467) having >2 hour journey. The out-of-pocket cost of travel was fairly /very burdensome for 22% patients (101/467), most noticeably those in Canada, Poland, and Turkey.

The hospital environment where patients received their trastuzumab was rated as fairly / very pleasant by most (445/467; 95%), and all agreed that the medical and nursing staff were fairly or very helpful. Patients found the SC sessions more acceptable (96%; 447/467) than their IV delivery of trastuzumab (80%; 375/467). IV delivery also lengthened the time patients reported spending at the hospital; 27% (128/467) spent over 3 hours in the clinic, compared to 12% (58/467) when receiving SC.

Method of administration

Chemotherapy and previous trastuzumab had been administered via cannula for 258/467 (55%) patients; other Venous Access Devices (VAD) such as in-situ PICCs or Ports 204/467(44%), and 5/467 (1%) had experienced both routes of administration prior to starting the study.

Just under half 120/263 (46%) reported that the staff had difficulty very often or sometimes when inserting cannulas and for 115/120 (96%) of these patients their final preference was for SC. Only 18/209 (9%) of women reported staff having any difficulty with other VADs but 15/18 (83%) still went on to prefer SC administration of trastuzumab. A small proportion (23/467, 5%) commented that some staff had difficulty with SC administration via the SID or HHS, but the final preferences of these women were 17 for SC administration, 5 for IV and 1 no preference.

Hypothetical preferences for type and setting

At the second interview, one section examined patients' preferences for administration of trastuzumab in different settings; patients were asked *"If you could choose IV or SC given at: - cancer centre or clinic, your local hospital, your GP or primary care physician's office or at your home by trained healthcare professionals which would you prefer?*

Figure 1 shows that the majority (282/467; 60%) preferred the idea of SC trastuzumab administration at home if it ever became available and the preference for this choice was very strong for 72% (204/282) and fairly strong for 22% (62/282) of women. Several patients made spontaneous comments illustrating reasons for preferences. Some reiterated the time and convenience factors associated with subcutaneous delivery generally e.g. "*With SC you gain time. It would be beneficial to have that at home with a specialist."* Others seemed to perceive not only convenience but also a potential psychological benefit e.g. *"As a patient I think Herceptin is marvellous, this advancement takes away 6 months of hospital visits. It diminishes the trauma. It would be ideal for patients to be able to do it at home",* and *"I believe that as cancer patients it's important to break away from the hospital. So if it can be done at home it's psychologically much better".* Only 4/467 (1%) women said they would prefer IV delivery at hospital. The main reason for this was that the staff there provided security as shown in this quote: *"I find it hard to choose between these two options. On one hand, it would be convenient to have it applied at home. On the other hand, I would feel safer if I was to receive the therapy at the medical institution. In my opinion, if anything went wrong, I would not be able to receive urgent advanced medical care immediately at home. Therefore, I would prefer to receive it at the medical institution."*

Question 61 Final Question

The final question **"***Are there any further comments you'd like to make about the different methods of giving the Herceptin treatments that you have had in the study?"* prompted 396 comments from 57% (267/467) patients; (Table 1). Twelve thematic categories were initially generated from these, which were later reduced down to 9 categories for the final coding and analysis. Comments were also classified as positive (305/396, 77%), negative (86/396, 22%) or neutral (7/396, 2%). The top 3 categories for Cohort 1 (SID) were to do with future delivery 45/215, (21%), compliments about the staff and or SC administration 35/215 (16%) and time/convenience issues 33/215 (15%). In Cohort 2 the top 3 were compliments 40/181(22%), future delivery 28/181 (15%) and practical considerations 28/181(15%).

Although the final question had aimed to elicit different responses from those made in support of the primary outcome (preference), many just wished to reiterate their two primary reasons for having chosen the SC method, namely that it was far less time consuming and convenient, less painful and more comfortable.

"Really like the fact that SC is quick"

"SC is a lot more comfortable"

"SC is a lot more pleasant, takes less time and can be done by a nurse"

Working women and those with young families expressed a need to get on with life after chemotherapy.

"I'm very happy with SC, the other is more unpleasant. Can't lead a normal life up to 24 hours afterwards, Need someone to look after my 2 girls"

Busy mum with four young children – want to get on with life"

The hospital environment and practical capabilities of the staff administering the drug may also have played a role in preferences. Table 2 shows both positive and negative comments about this, for example, some staff, despite a study requirement for them to have viewed a training DVD and/or be proficient in SC delivery, lacked confidence or expertise in administering the drug this way. Incompetence can be painful and have an additional impact on a patient's psychological well-being.

"The first time I had it the person who administered it hadn't been trained properly and they did it too quickly, so it was painful and this caused my anxiety before the remaining SC sessions. " (HHS)

Gratitude was expressed by several women for the opportunity to participate in the PrefHer trial and to experience SC delivery of trastuzumab.

"The study was very pleasant. One was treated well and one had the feeling of safety and trust. We were well looked after"

"Content with everything and happy to have been able to participate so that it hopefully can help others"

"I'm very pleased to have taken part in the study. SC is very much better. Psychologically it's difficult to go on to IV Herceptin after having completed chemotherapy."

Discussion

Information from PROs such as patient preferences gathered via well-conceived study specific interview schedules may refine and influence doctor/patient decision-making but few trials conducted to date have outcome measures such as these as primary outcomes. The design of the PrefHer trial provided an ideal opportunity to explore patients' views in more depth than is

usual in clinical trials about different aspects and experiences associated with different methods of trastuzumab administration.

Any extra survival time achieved through treatment needs to be balanced against the efforts and burdens required when otherwise efficacious drugs are administered. Time is a precious commodity to patients with cancer and although some find regular contact and support from healthcare professionals valuable, a majority would prefer to spend less time waiting around in the much pressured environment of a busy chemotherapy centre.

There are significant practical advantages besides the obvious convenience for patients and healthcare professionals; SC is a useful alternative to patients with poor venous access, circumvents anxieties about extravasation with cannulation and solves the problems associated with in-situ VADs including blockages and infection. It also saves pharmaceutical preparation time. Time & Motion studies have been conducted demonstrating the favourable cost efficacy of SC compared with IV trastuzumab in the hospital setting [9]. The way that economic costs are processed by cancer centres may limit the uptake of ambulatory delivery of trastuzumab and self-administration in appropriate patients, but this surely will eventually to lead to an overall reduction in healthcare costs. The results from the ongoing SafeHer study (NCT01566721) will provide more data not only about safety and tolerability of SC trastuzumab given either by HHS or by SID, but will also show how satisfied patients are with self-administration using the SID. Another study, ChangHer is looking at IV versus SC trastuzumab in the metastatic breast cancer setting.

The PrefHer study was global and yet, irrespective of culture, the primary outcome was the same, with patients expressing a strong and compelling preference for SC delivery. The main reasons given for these preferences were perceived convenience and time saving which were

perhaps all the more surprising as the PrefHer trial protocol mandated extra procedures that might not have been needed out with a trial setting.

Although in PrefHer many staff involved were experienced chemotherapy nurses, the study did reveal the importance of good, quality training. The overwhelming preference of most patients for SC over IV made us examine more closely the reasons given by those who still preferred IV. It was clear that if the SC formulation was administered too quickly, a problem with the HHS not the SID, then patients could find it painful. Likewise if staff were unfamiliar with placement of the SID then administration could be complicated and/or patients become anxious.

In conclusion, the need for long-term trastuzumab treatment, necessitating hospital visits every 3 weeks for a year, is not a pleasant prospect for women with breast cancer who have completed their surgery, and other adjuvant therapy and just want to resume normal life. The development of a quick and easy method of SC trastuzumab delivery goes some way to minimising the disruption to everyday living, enhancing quality of life.

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Table 1: Responses to Question 61 *"Have you any other comments?"*

Cohort 1 N= 137/236; patients made 215 comments: 172 positive; 40 negative; 3 neutral (57/137 made multiple comments)

Cohort 2 N= 130/231; patients made 181 comments: 131 positive; 46 negative; 4 neutral (44/130 made multiple comments)

	Cohort 1				Cohort 2				Combined			
	+ ve	**- ve**	**-**	**n**	**+ ve**	**- ve**	**-**	**n**	**+ ve**	**- ve**	**-**	**n**
Compliments	35	0	0	**35**	40	0	0	**40**	**75**	**0**	**0**	**75**
Future Delivery	43	2	0	**45**	27	0	1	**28**	**70**	**2**	**1**	**73**
Practical	14	16	2	**32**	10	17	1	**28**	**26**	**33**	**3**	**60**
Time /convenience	32	1	0	**33**	16	4	1	**21**	**48**	**5**	**1**	**54**
Pain/discomfort	20	6	0	**26**	11	3	0	**14**	**31**	**9**	**0**	**40**
Study	11	3	0	**14**	12	4	1	**17**	**23**	**7**	**1**	**31**
Side effects	3	10	0	**13**	5	12	0	**17**	**8**	**22**	**0**	**30**
Psychological	11	1	0	**12**	7	5	0	**12**	**18**	**6**	**0**	**24**
Efficacy	3	1	1	**5**	3	1	0	**4**	**6**	**2**	**1**	**9**
Totals	**172**	**40**	**3**	**215**	**131**	**46**	**4**	**181**	**305**	**86**	**7**	**396**

+ ve positive comment

- ve negative comment

- neutral

Table 2: Examples of positive, negative and neutral quotes for the 9 categories		
	SID – subcutaneous I device; HHS – hand held syringe;	
Category	**Examples of positive comments**	**Negative and Neutral Examples**
Compliments	My preference of SC therapy is very big! I loved the SC therapy. I would like to praise the staff at the research chemo unit. They were very helpful and made treatment as comfortable and convenient as possible. I could take my children with me if I needed to.	
Future delivery	Reason for doing the trial was so that other women hopefully will be able to have the device. It's brilliant and I'd like to do it myself at home! (SID)	SC I like a lot, but I don't want to do it myself or through carers at home. Communication with doctors in the oncology practice is very important to me in case I have questions.(HHS)
Practical Issues	SC is less constraining than IV, there is no "patch" to wear, no blockages	Could the nurses have an arm support when giving the injection? It hurts if they move the needle during the injection but they find it hard to hold their arm still for 5 minutes. (HHS)
Time/convenience	Really like the SC and the fact it is quick. (SID) I found SC better for me because it was just one injection and that was it. (HHS)	1 Hour waiting time for warming up the medicine is a bit too much.
Pain/discomfort	SC treatment was very quick, painless and convenient. (SID) They shouldn't just have given us 4 SC but all of them. Much more comfortable and the staff are just super. (HHS)	With SC I felt a bit of pain in the leg in the area around were they pricked me. (HHS) I think the nursing staff touched a muscle, it was on my thigh and it was painful when walking, very painful actually. Also, with SC I think it would be better to do it in five minutes, a bit more slowly, because when it takes 3-4 minutes it is painful.

Study	For me Herceptin with the SC method was an undreamed-of solution. With the IV method I had to have a port. I am extremely happy to have agreed to take part in this trial. It was like liberation for me. (SID) No further comments, apart from the fact that I am very pleased to have been asked to take part in this trial. Also, both the medical and the paramedical staff looked after me very well.(HHS) I'm very satisfied to have been part of the study and feel that you properly get looked at more by the doctors. (HHS)	I see myself unsure. Both have advantages and disadvantages. Both are good. SC, one is a bit disturbed by the fact that it's individual to a nurse so it depends on the nurse and this gives one a funny feeling, but it's good that it's quick. I've also heard that equipment instead of an injection exists and I find this better.
Side effects	IV, overall, I had difficulties to fall asleep whereas SC method spread more slowly then I felt plenty of energy.	Tiredness is one of the things I get troubled by still and when I have it SC the tiredness hits me in one swoop (in an hour). When I have it IV the tiredness spreads over 2 to 3 days. (SID) Too many allergies during 1 week after each injection that I have not experienced with the VAD (HHS)
Psychological	I would love to continue it this way. It's very pleasant, less psychological burden. With IV one sits in the same room with patients receiving chemo this doesn't make one feel very good	The first time I had it the person who administered it hadn't been trained properly and they did it too quickly, so it was painful and this caused my anxiety before the remaining SC sessions.(HHS) I just find SC unpleasant simply because of my fear of injections.
Efficacy	I think it works better this way (SC)	I wonder if Herceptin works in the same way no matter which method of application is used. As a doctor I guess that IV method more effective than SC.

Figure 1: Patients' responses to hypothetical scenario of future delivery of trastuzumab

Combined cohorts n= 467