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Original article

Switching between intravenous and subcutaneous trastuzumab: Safety results from the PrefHer trial

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ABSTRACT

Aim: To assess the safety and tolerability of switching between subcutaneous (SC) and intravenous (IV) trastuzumab in the PrefHer study (NCT01401166).
Patients and methods: Patients with HER2-positive early breast cancer completed (neo)adjuvant chemotherapy and were randomised to receive four cycles of SC trastuzumab, via single-use injection device (SID; Cohort 1) or hand-held syringe (Cohort 2), followed by four cycles of IV, or vice versa (the crossover period presented here) as part of their 18 standard cycles of adjuvant trastuzumab treatment. Adverse events (AEs) were reported using standard criteria.
Results: Overall, fewer AEs were reported during the IV treatment periods, regardless of administration sequence (IV→SC or SC→IV). Differences in AEs between the SC and IV periods were partly due to variances in grade 1 and 2 local injection site reactions (ISRs) and systemic administration-related reactions (ARRs) and these occurred mainly during SC treatment, as expected. When ISRs and ARRs were excluded, rates of AEs were higher during the first treatment period, compared with the second, in both treatment sequences; otherwise there was no clear pattern in the type of AEs reported. Rates of clinically important events, including grade ≥3 AEs, serious AEs, AEs leading to study drug discontinuation and cardiac AEs, were low and similar between treatment arms (<5%). There were no grade 4 or 5 AEs. No new safety signals for trastuzumab were observed.
Conclusions: PrefHer revealed that switching from IV to SC trastuzumab (hand-held syringe or SID) or vice versa did not impact the known safety profile of trastuzumab.

1. Introduction

Trastuzumab (Herceptin®, F. Hoffmann-La Roche Ltd, Basel, Switzerland), is the standard of care for treating human epidermal growth factor receptor 2 (HER2)-positive breast cancer [1–3] and can be administered by intravenous (IV) infusion or subcutaneous (SC) injection. SC trastuzumab (Herceptin® SC, F. Hoffmann-La Roche Ltd) contains the recombinant human hyaluronidase enzyme as an excipient and offers a fixed-dose alternative to the conventional weight-adjusted IV dose. SC trastuzumab was approved by the European Medicines Agency based on data from the phase III, open-label, randomised, international HannaH study (NCT00950300) [4,5].

HannaH compared SC and IV trastuzumab in terms of

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pharmacokinetics, efficacy and safety in the neoadjuvant–adjuvant setting [4,5]. Analysis of the co-primary endpoints, serum trough concentration (C_{trough}) and pathological complete response (pCR), demonstrated that SC trastuzumab was non-inferior to IV [4]. Despite similar overall safety profiles, a numerical difference was reported in the rate of serious adverse events (SAEs) [4,5]. This imbalance was not reflected in the distribution of grade 3–5 AEs, and despite systematic analyses an underlying clinical explanation could not be identified [4,5]. An SC trastuzumab single-use injection device (SID) demonstrates pharmacokinetic bioequivalence with the hand-held syringe method [6].

Patients' preferences, for either SC administration or IV infusion, were investigated in the international, open-label, randomised, two-cohort, two-arm, PrefHer study (NCT01401166) in HER2-positive early breast cancer [7–9]. PrefHer incorporated a unique crossover period, comprising four cycles of SC trastuzumab followed by four cycles of IV, or vice versa. This study design allowed a direct comparison of patients' preferences for SC or IV trastuzumab and evaluation of the safety profile associated with multiple, sequential administrations.

When compared with the known safety profile of IV trastuzumab, previous analyses from both cohorts of PrefHer indicated that SC trastuzumab was well tolerated, with no new safety signals [7–9]. Although an increase in clinician-reported AEs was noted with SC trastuzumab, this was not the case for patient-reported events [7,9]. Differences between AE rates in the combined SC and IV periods (Cohorts 1 and 2) were driven by grade 1 events and occurred more frequently during the SC period [7,9]. However, patients preferred SC over IV trastuzumab regardless of SID or hand-held syringe delivery, and patients reported SC trastuzumab to be less painful and to cause less bother from bruising or irritation than IV [7–9].

With consistent patient preference for SC over IV trastuzumab and the European approval of SC trastuzumab, patients may opt to switch from IV to SC trastuzumab during their treatment for early breast cancer. Due to its unique design, the PrefHer study offered the opportunity to assess the safety profile of patients switching between IV and SC trastuzumab, considering not only the influence of the treatment sequence, but also the impact of previous exposure to IV trastuzumab during (neo)adjuvant treatment. We report the results of this analysis here.

2. Patients and methods

2.1. Patients and study treatment

After completion of surgery and neoadjuvant or adjuvant chemotherapy, patients were randomised to receive four cycles of SC trastuzumab followed by four cycles of IV trastuzumab, or vice versa (the crossover period assessed here; Fig. 1) [7–9]. Patients then received trastuzumab to complete their standard 18 cycles of adjuvant treatment, planned to be via IV or SC SID in Cohort 1 and SC hand-held syringe in Cohort 2. Since (neo)adjuvant treatment could have included prior IV trastuzumab, randomisation was stratified by de novo (trastuzumab-naïve) or non-de novo (already receiving IV trastuzumab) treatment. Patients were enrolled if they still had at least eight out of their 18 planned cycles of trastuzumab remaining.

SC trastuzumab was administered either via SID (Cohort 1) or hand-held syringe (Cohort 2) and given every 3 weeks at a fixed dose of 600 mg, with no loading dose required. IV trastuzumab was administered every 3 weeks at a loading dose of 8 mg/kg (if the patient was not already receiving trastuzumab and was randomised to receive IV trastuzumab as the first cycle of treatment), followed by maintenance doses of 6 mg/kg.

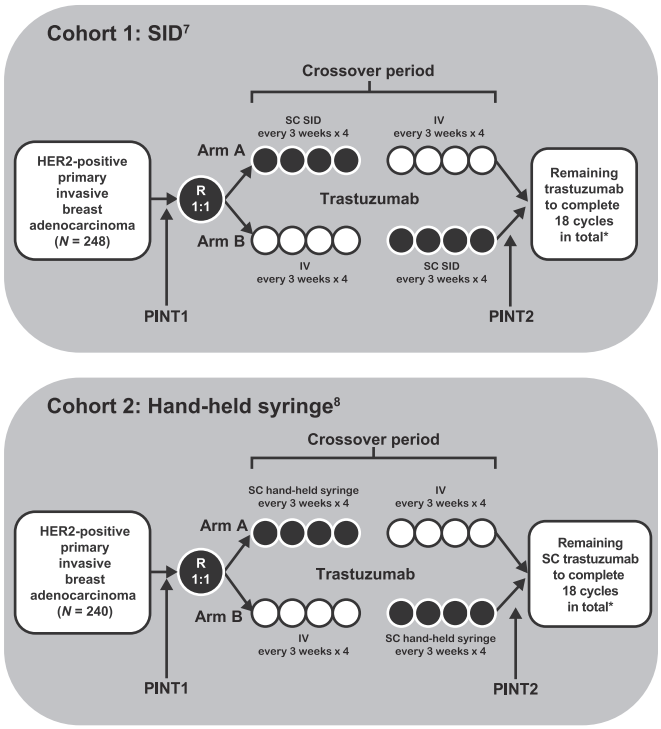

Fig. 1. PrefHer study design. Includes optional time-and-motion sub-study in both cohorts [10,11]. Patients completed surgery and (neo)adjuvant chemotherapy (concurrent or sequential with IV trastuzumab) and had at least eight out of the total of 18 planned trastuzumab cycles remaining in their adjuvant trastuzumab therapy. Stratification factor: de novo versus non-de novo trastuzumab (to balance the sequence groups for the proportion of patients with prior IV trastuzumab treatment). * In the SID cohort, remaining trastuzumab was administered by IV infusion unless patients participated in SID self-administration. In the hand-held syringe cohort, remaining trastuzumab was planned to be administered subcutaneously by hand-held syringe. **Abbreviations:** HER2, human epidermal growth factor receptor 2; IV, intravenous; PINT, patient interview; R, randomised; SC, subcutaneous; SID, single-use injection device.

The primary endpoint, previously reported, was the proportion of patients indicating an overall preference for SC or IV trastuzumab administration [7,9]. Secondary endpoints included safety and tolerability [7–9].

PrefHer was conducted 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.

2.2. Assessment of switching between SC and IV trastuzumab

AEs that occurred during the crossover period were summarised according to the primary system-organ class (SOC), and within each SOC by Medical Dictionary for Regulatory Activities (MedDRA)-preferred term; including overall AEs, grade ≥3 AEs, SAEs, systemic administration-related reactions (ARRs), localised injection site reactions (ISRs), AEs leading to discontinuation and cardiac AEs. AE incidences were summarised by treatment sequence (IV→SC or SC→IV) and route of administration (SC or IV); rates of AEs were then summarised by cohort (Cohort 1 or 2 and combined) and de novo or non-de novo trastuzumab. Analyses either included or excluded ARRs and ISRs.

AEs, SAEs and cardiac AEs were graded and reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V4.0), International Conference on