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Original Research

Patients' preference of trastuzumab administration (subcutaneous versus intravenous) in HER2-positive metastatic breast cancer: Results of the randomised MetaspHer study

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Abstract HannaH (NCT00950300) and PrefHer (NCT01401166) studies validated the subcutaneous (H-s.c.) formulation of trastuzumab as effective and safe as intravenous (H-i.v.) and highly preferred by patients in early breast cancer. The present randomised MetaspHer trial (NCT01810393) is the first study assessing patient's preference in metastatic setting.
Methods: Patients with HER2-positive metastatic breast cancer who completed a first line chemotherapy with trastuzumab and achieved a long-term response lasting more than 3 years were randomised to receive 3 cycles of 600-mg fixed-dose adjuvant H-s.c., followed by 3 cycles

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of standard H-i.v., or the reverse sequence. Primary end-point was overall preference for H-s.c. or H-i.v. at cycle six, assessed by Patient Preference Questionnaire (PPQ). Secondary end-points included healthcare professional (HCP) satisfaction; safety and tolerability; quality of life.

Results: Hundred and thirteen patients were randomised and treated. H-s.c. was preferred by 79/92 evaluable intent-to-treat patients (85.9%, 95% confidence interval [CI; 78.8–93.0]; $p < 0.001$), 13/92 preferred H-i.v. (14.1%, 95% CI [7.0–21.3]). HCPs were most satisfied with H-s.c. (56/88 available data, 63.6%, [53.6–73.7]). On the safety population, adverse events occurred in 73 (67.6%) and 49 (44.1%) patients during the H-s.c. and H-i.v. periods, respectively; 7 (6.5%) and 4 (3.6%) were grade $\geq$ III, 3 (2.8%) and 2 (1.8%) were serious.

Conclusion: The safety was consistent with the known H-i.v. and H-s.c. profiles without safety concern raised. Definitively, patients preferred H-s.c. as reported in early stage by PrefHer study.

1. Introduction

Trastuzumab represents a clinical breakthrough in treating human epidermal growth factor receptor 2 (HER2)—positive breast cancer, significantly increasing survival in the adjuvant setting and constituting the keystone of treatment for metastatic breast cancer (MBC) [1–6]. Since 2013, 600-mg fixed-dose manual injection of subcutaneous trastuzumab (Herceptin® s.c., F. Hoffmann-La Roche Ltd, Basel, Switzerland) (H-s.c.) was approved by the European Medicines Agency as an alternative to conventional Herceptin® intravenous (H-i.v.) infusion, based on results of the randomised phase III HannaH study [7–9]. This trial demonstrated superimposable efficacy based on pathological complete response in neoadjuvant setting and demonstrated similar pharmacokinetics results especially in terms of concentration through the key pharmacokinetics end-point for trastuzumab biological activity. PrefHer study emphasised the preferences of patients in the adjuvant breast cancer setting for H-s.c. delivery [10,11]. Currently, H-s.c. formulation is as effective than the H-i.v. formulation and appeared to be the preferred option by patients. We present additional results of patient preferences in the metastatic setting through the present randomised MetaspHer study (NCT01810393) conducted under the Umbrella programme assessing safety and tolerability of H-s.c. through eight prospective clinical studies.

2. Methods

Patients with HER2-positive (immunohistochemistry 3+ or positive by *in situ* hybridisation) metastatic breast cancer who completed a first line chemotherapy with trastuzumab (H-i.v.) and achieved a long terms response lasting more than 3 years were eligible. Additional main inclusion criteria included: older than 18 years; an Eastern Cooperative Oncology Group performance status of 0 or 1; a baseline left ventricular ejection fraction (LVEF) higher than 50% measured over the 3 months before inclusion; no progressive disease assessed by clinical exam, CT-scan and bone scan observed within 3 weeks prior the inclusion. Patients were randomised 1:1 using randomly permuted blocks of four to receive 3 cycles of 600-mg fixed-dose H-s.c. injected into the thigh over approximately 5 min, followed by 3 cycles of standard H-i.v. (6 mg/kg over 30–90 min), or the reverse sequence (Fig. 1). Randomisation was performed via central interactive voice-recognition or interactive web-based response systems. Following the crossover period patients could receive H-s.c. or H-i.v. formulation according to their choice until disease progression. Safety was evaluated at each cycle, LVEF and disease assessments were scheduled every 18 weeks over a one-year period then every 6 months.

Primary end-point was overall preference for H-s.c. or H-i.v. at cycle six, assessed by Patient Preference Questionnaire (PPQ). Secondary end-points included healthcare professional (HCP) satisfaction, assessed by questionnaire; safety and tolerability, assessed by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0; quality of life assessed by Quality of Life Questionnaire Core30 (QLQ C30) questionnaire, Assessment of factors influencing patient preference was an exploratory end-point including items from the baseline questionnaire and patients characteristics.

The intent-to-treat (ITT) population included patients who received both routes of administration and who completed the last question of PPQ. The safety population included all enrolled patients who received at least one dose of treatment.

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