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Clinical Trial

HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant–adjuvant trastuzumab after 2 years of treatment-free follow-up

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Abstract ***Background:*** In the phase III, open-label, randomised HannaH study, fixed-dose neoadjuvant–adjuvant subcutaneous trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer was non-inferior to standard weight-based intravenous infusion in terms of serum trough concentration and pathological complete response (pCR). Evidence suggests that pCR, particularly total pCR (tpCR), is likely to predict clinical benefit. We report associations between tpCR and event-free survival (EFS) from HannaH (the largest population from a single study of patients presenting with newly diagnosed HER2-positive breast cancer treated with neoadjuvant–adjuvant trastuzumab to date) plus long-term efficacy and safety.

Methods: Eligible patients received four cycles of neoadjuvant docetaxel followed by four cycles of fluorouracil/epirubicin/cyclophosphamide administered concurrently with 3-weekly subcutaneous (600 mg fixed dose) or intravenous trastuzumab (8 mg/kg loading, 6 mg/kg maintenance doses). Post-surgery, patients received adjuvant trastuzumab as randomised to complete 1 year of standard treatment. In exploratory analyses, we used Cox regression to assess associations between tpCR and EFS. EFS rates per subgroup were estimated using the Kaplan–Meier method.

Findings: Three-year EFS rates were 76% for subcutaneous and 73% for intravenous trastuzumab (unstratified hazard ratio [HR] 0.95, 95% confidence interval [CI] 0.69–1.30; intention-to-treat population). Three-year overall survival rates were 92% for subcutaneous and 90% for intravenous trastuzumab (unstratified HR 0.76, 95% CI 0.44–1.32). tpCR was associated with a reduced risk of an EFS event: subcutaneous arm HR 0.38 (95% CI 0.22–0.65); intravenous arm HR 0.32 (95% CI 0.18–0.60). Results were similar for subgroups, including oestrogen receptor status. The few additional adverse events occurring during treatment-free follow-up were balanced between arms.

Interpretation: Long-term efficacy supports the established non-inferiority of subcutaneous trastuzumab, and its safety profile remains consistent with the known intravenous profile. In each of HannaH's treatment arms, tpCR was associated with improved EFS, adding to evidence that tpCR is associated with clinical benefit in HER2-positive early breast cancer.

1. Introduction

One year of subcutaneous trastuzumab (Herceptin® SC; F. Hoffmann-La Roche Ltd, Basel, Switzerland) is approved in over 60 countries worldwide as neoadjuvant and adjuvant therapy for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, and its advantages over intravenous trastuzumab (Herceptin®, F. Hoffmann-La Roche Ltd) include time savings and convenience for patients and health care professionals [1–3]. Patients reported preference for subcutaneous trastuzumab because it saves time and, in contrast with clinically reported adverse events, causes less pain/discomfort/side-effects [3–5]. Approval of subcutaneous trastuzumab was based on results of the HannaH phase III study; with almost 600 patients, HannaH is the largest single study in patients with HER2-positive early breast cancer homogeneously treated with neoadjuvant–adjuvant trastuzumab. HannaH confirmed non-inferiority of subcutaneous versus intravenous trastuzumab in terms of the co-primary end-points of serum trough concentration (C_{trough}) and pathological complete response (pCR) [6]. Additional analyses at 20 months' median overall follow-up confirmed the 12-month analysis finding that subcutaneous trastuzumab was generally well tolerated, with adverse event and event-free survival (EFS) rates comparable to those seen with intravenous trastuzumab [7]. We now report per-protocol long-term efficacy (EFS and overall survival [OS]) and safety from the HannaH study with a median overall follow-up of approximately 40 months, after the last patient had completed 1 year of neoadjuvant–adjuvant treatment and at least 2 years of additional treatment-free follow-up (clinical cut-off). HannaH's study design also allowed exploratory analyses of the association between pCR and EFS. Prior studies have indicated that pCR, and in particular total pCR (tpCR; absence of invasive neoplastic cells in the breast and ipsilateral lymph nodes, regardless of ductal carcinoma in situ), is likely to predict clinical benefit in patients with HER2-positive early breast cancer [8–14]. Moreover, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) define pCR as the absence of cancer in the breast and ipsilateral (regional) lymph nodes [15,16]. This definition is equivalent to the definition of tpCR in HannaH. Thus, tpCR is used for the main association analyses here.