Pharmacokinetic results of a subcutaneous injection of trastuzumab into the thigh versus into the abdominal wall in patients with HER2-positive primary breast cancer treated within the neo-/adjuvant GAIN-2 study

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A subcutaneous (s.c.) formulation of trastuzumab became available in 2013 based on equivalent efficacy, pharmacokinetics (PK) and safety with standard intravenous (i.v.) administration. In this study, s.c. trastuzumab was administered into the thigh or the abdomen. As an s.c. injection into the abdominal wall (abdw) might be more convenient for patients (pts) and health care professionals, the PK profile of s.c. trastuzumab injected into the thigh vs into the abdw in pts with HER2-positive early breast cancer needs to be evaluated.

Study design of the GAIN-2 main trial including the s.c. trastuzumab substudy is shown in Figure 1. Based on the variability observed in the HannAH study1 and using a total sample size of 36 (15 per arm) pts, the estimated two-sided 90% CI of the plasma concentration-time curve (AUC0-t) was (0.79-1.27) and (0.77-1.30) of the peak drug concentration (CMAX) respectively. For allowing for a dropout rate of 15%, 18 pts per group were planned to be included in the substudy. For the PK profile of s.c. trastuzumab, blood samples collected before cycle 7, on days (d) 2, 4, 8, 15 and 21 of cycle 7 were evaluated.

One-way analyses of covariance were performed to compare PK parameters between the two routes of administration and adjusted for body weight at baseline including stratification factors based on the respective trial (protocol) analysis set. Routes of administration could be considered comparable if the observed two-sided 90% CIs of the geometric mean ratio (GM-R) are similar to the estimated CI.

Objectives

- Primary objective: to assess the PK profile of s.c. trastuzumab injected into the thigh vs into the abdomen using the peak exposure (Cmax) of trastuzumab (taken directly from the data without interpolation) and the extent of exposure (AUC0-t) from day 0 to day 21.
- Secondary objective: to assess the peak drug plasma concentration (Cmax) and drug concentration at the end of the dosage interval (Cint,day6) safety and tolerability.

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Figure 1: Study design of the GAIN-2 main trial and s.c. trastuzumab substudy

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Table 1. Characteristics of patients

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<th>Low</th>
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<tr>
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<td>Stage</td>
<td>n (%)</td>
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</table>

The pp-set consisted of 30 pts (17 in the thigh and 13 in the abdw). Baseline characteristics are shown in Table 1. The mean plasma concentration-time profiles of the s.c. trastuzumab administered into the thigh and into the abdw are presented in Figure 2. The geometric mean ratios (GM-R) for Cmax, AUC0-t, Cint and Cint,day6 were (1.00-1.12). Acceptable variability by measured by CV for Cmax, AUC0-t, Cint and Cint,day6 was observed in the thigh group (Table 3).

Conclusions

- Bioavailability of the s.c. trastuzumab as reflected by peak and total exposure measured in cycle 7 was approximately 30% higher if administered into the thigh rather than into the abdominal wall in pts with HER2-positive primary breast cancer treated with dose-dense CT plus i.v. trastuzumab.
- PK parameters of the s.c. trastuzumab administered into the thigh were in line with those from the HannAH study1.
- No increased toxicity was observed in both treatment groups.
- Study limitations were that no cross-over design was used and the number of patients satisfying criteria for pp-set were different in the groups.

References