

INTRAVENOUS VERSUS SUBCUTANEOUS TRASTUZUMAB IN THE TREATMENT OF BREAST CANCER

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Background and objective

- Breast cancer (BC) is the most common cancer in women worldwide; it has an unquestionable negative impact on the public health of the modern societies.
- Trastuzumab (TZ), a recombinant antibody targeting the human epidermal growth factor receptor (HER) 2, was the first biological drug approved for the treatment of HER2-positive BC and remains the gold-standard for this indication.
- Currently, TZ is available in intravenous (IV) and subcutaneous (SC) formulations; clinicians are routinely confronted with the difficult of selecting the best administration route for this drug .
- This work aims to clarify which administration route is preferable for TZ in the treatment of BC.

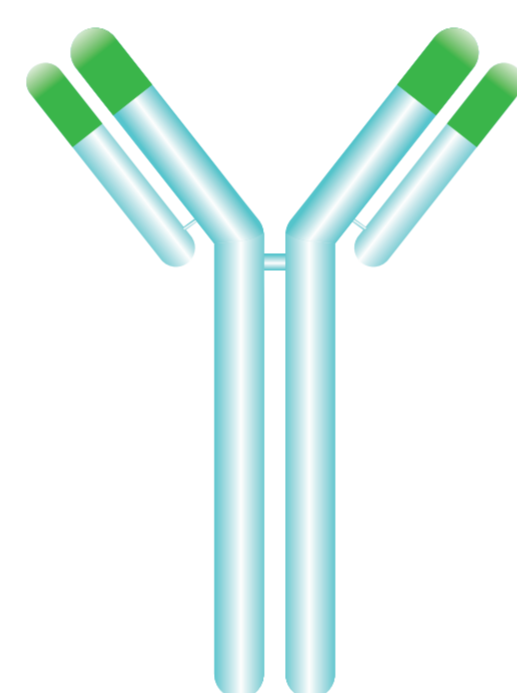


Figure 1: Structure of the humanised monoclonal antibody trastuzumab (TZ)

Method

- Literature review. PubMed database was searched for clinical studies published in the last five years, using combinations of the keywords: “breast cancer”, “intravenous trastuzumab” and “subcutaneous trastuzumab”.

Results

- IV doses of TZ should be adjusted to the body weight whilst the SC formulation has an approved dosing schedule of 600 mg every three weeks, irrespective of patients’ body weight [1]. Actually, several studies have suggested that the body size does not significantly influence the pharmacokinetics of TZ [2-4].
- The SC administration does not require a loading dose, given that the first dose results in therapeutic concentrations [2-4].
- Two recently published studies on the comparison of the two formulations deserve attention: the [HannaH study](#) [5] and the [PreffHer study](#) [7].

HannaH study

- Randomised phase 3 study with the aim of demonstrating the non-inferiority of SC TZ in relation to IV TZ at the pharmacokinetics and pharmacodynamics level. The study enrolled 596 patients with HER2-positive BC that received SC or IV TZ randomly at every three weeks.
- Mean serum concentrations achieved for IV and SC groups were similar (1st cycle: 34,5 µg/ml versus 32,7 µg/ml; 3rd cycle: 45,0 µg/ml versus 48,4 µg/ml, respectively).
- However, it was verified a **higher fluctuation index for SC TZ**:
 - Mean C_{min} was higher in the 8th and 13th cycle for patients treated with SC TZ (78,7 µg/mL and 90,4 µg/mL respectively) compared to IV TZ (57,8 µg/mL and 62,1 µg/mL respectively);
 - Mean C_{max} was lower in the group of SC TZ (149 µg/mL versus 221 µg/mL).

- Steady state concentrations were first achieved for IV TZ (8th cycle versus 13th cycle).
- The **SC formulation was non-inferior** with respect to the primary pharmacokinetics endpoint, the mean C_{min} measured after seven cycles.
- There was **comparable efficacy** for the two routes, as shown by the proportion of patients who achieved pathological complete response: 118 out of 260 (SC TZ) and 107 out of 263 (IV TZ).
- No significant differences were observed in the safety profile, although the subcutaneously-treated group reported more adverse effects (21% versus 12%), particularly infections and infestations.

The SC formulation contains recombinant human hyaluronidase to overcome absorption barriers, which reduces the administration duration and removes the need to establish intravenous access, thus improving the overall convenience of TZ administration [5].

PreffHer study

- A randomized study that evaluated the patient preference between the two TZ administration routes in 248 patients.
- 92% of the patients chose the SC option as the preferred administration route, due to time saving, less pain/discomfort, ease of administration and more convenience.
- The remaining 8% of patients justified to prefer the IV route mainly due to the less pain, bruising and irritation associated to the administration.

Table 1: Overview of the IV SC and SC routes for trastuzumab (TZ)

Route	Intravenous (IV)	Subcutaneous (SC)
Maintenance dose	<ul style="list-style-type: none">Three weekly schedule- 6mg/kgWeekly schedule - 2 mg/kg	Fixed dose of 600 mg every three weeks
Loading dose	<ul style="list-style-type: none">Three weekly schedule - 8 mg/kgWeekly schedule - 4mg/kg	Not required
Time of administration	Loading dose: 90 minutes Following doses: 30 minutes	2-5 minutes
Pharmacokinetics profile	Bioequivalent	
Efficacy and safety profile	Similar	

Conclusions

- The available evidence supports the **pharmacokinetics and pharmacodynamics bioequivalence** of the SC and IV administration of TZ.
- TZ subcutaneously is **more cost-effective** and **more convenient** for patients.
- Therefore, the SC route is currently the best option for the administration of TZ in the treatment of HER2-positive BC and its adoption as the standard route of administration is probably a matter of time.

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