The socio-economical impact of intravenous (IV) versus subcutaneous (SC) administration of trastuzumab: future prospectives

K. Papadmitriou, X.B. Trinh, S. Altintas, P.A. Van Dam, M.T. Huizing, W.A.A. Tjalma*

Antwerp University Hospital and University of Antwerp, University Multidisciplinary Breast Clinic and Gynecological Oncology Unit, Wilrijkstraat 10, 2650 Edegem, Belgium.
*Correspondence at: Wiebren.Tjalma@uza.be

Abstract

Trastuzumab was the first targeted therapy for HER2 positive breast cancer. It has become the standard of care for HER2 positive metastatic breast cancer since 2000 and in the adjuvant setting since 2006. Adjuvant it is given for a year and in patients with metastatic disease until progression. The standard mode of administration is intravenous. Recently a subcutaneous form has become available. A phase III study showed that there is no difference between the intravenous and subcutaneous form in terms of safety and efficacy. The patient’s preference however significantly favoured the subcutaneous form. It is estimated that the use of the SC form could contribute to a cost saving between 758 and 2576 euro per annual course. For Belgium alone this could mean an estimated saving of 1.4 to 4.6 million euros per year. The potential benefit of the SC administration for healthcare facilities could be further increased when applied in a LEAN working day-care chemotherapy unit. After reviewing the existing literature we suggest to further validate the potential financial impact of SC trastuzumab compared to the traditional IV form and to introduce a scientific proposal incorporating the benefits of this formulation in a LEAN working healthcare unit.

Key words: Breast cancer, economical savings, intravenous, subcutaneous, trastuzumab, LEAN.

Introduction

HER2/neu oncoprotein is overexpressed in 1 out of 6 of all breast cancers (Vu et al., 2014). The overexpression leads to increased cell proliferation and neovascularization, which is associated with a poor prognosis. Trastuzumab became the first Food and Drug Administration-approved targeted therapy for HER2 positive breast cancer. Multiple randomized controlled trials showed that adding trastuzumab to chemotherapy in early or metastatic breast cancer is very successful and based on these trials it became standard of care in the metastatic setting since 2000 and in the adjuvant setting in 2006 (Piccart, 2001; Piccart-Gebhart et al., 2005; Arteaga et al., 2011; Slamon et al., 2011). In all these trials trastuzumab was administrated intravenously (IV), in a weekly or 3-weekly schedule, with a weight-based dose calculation and with a loading dose approach. Neither the weight-based dosing nor the use of a loading dose proved to be of clinical significance (Leveque et al., 2008).

Recently a subcutaneous (SC) form of trastuzumab was introduced. A phase 1/1b study, pharmacokinetics comparison between the SC and the IV form, proved that trastuzumab formulated with hyaluronidase appears to be well absorbed after subcutaneous injection, while the terminal half-lives were similar after IV and SC injection (Wynne et al., 2013). In this study, patients with HER2-positive breast cancer and healthy male volunteers were treated with the two formulations. Males were used, in order to avoid exposing healthy females at the risk of developing anti-trastuzumab antibodies. The efficacy and safety of the SC formulation was positively validated in non-inferiority multi-centre randomized phase III trial (HannaH) (Ismael et al., 2012). In the trial there was an imbalance in the reported serious adverse events but this was not reflected in the incidence of severe
adverse events, which was the same in both study groups. An updated report of this trial validated the safety profile of SC trastuzumab, as it remained consistent with the previously published data and the known safety profile of IV trastuzumab, while event free survival rates were comparable between the IV and SC groups (Jackisch et al., 2015).

An additional benefit for the SC versus IV trastuzumab for both patients and health care professionals was recently reported in an international, randomized, two-cohort study (PrefHer) (Pivot et al., 2013, Pivot et al., 2015). The primary endpoint was patient’s overall preference; secondary endpoints included healthcare professional’s satisfaction, safety, event-free survival and immunogenicity. As a result, 92% of patients favoured the SC form, as this approach saved time and was related to less pain and discomfort. The secondary endpoints also favoured SC administration. The SC form was well tolerated and safety was consistent with the previous reports. Both the PrefHer and HannaH study indicate that SC trastuzumab is a validated and preferred option over IV for improving patients’ care in HER2 positive breast cancer.

In parallel to the PrefHer study, the “time & motion” study, a small, UK based trial, validated a potential benefit in terms of cost and time spared, associated with the administration of SC trastuzumab compared to the traditional IV form. (Burcombe et al., 2013). Despite the impressive results, this study remains the only trial published in a peer-reviewed journal focusing on the socio-economical aspect of this approach.

The potential benefit of the SC administration for healthcare facilities could be further increased when applied in a LEAN working day-care chemotherapy unit. The goal of this review is to further validate the potential financial impact of SC trastuzumab compared to the traditional IV form and to introduce a scientific proposal incorporating the benefits of this formulation in a LEAN working healthcare unit.

Methods

The Pubmed, Embase, Elsevier Biobase and Cochrane databases were systematically searched (last access on June 1, 2015) for studies using the terms trastuzumab, administration, intravenous and subcutaneous. All the cross-references were also checked.

Results

In total only 2 studies were identified focusing in the use of healthcare resources in relation to SC or IV administration of trastuzumab: the previously mentioned time & motion study (Burcombe et al., 2013) and one trial originating from the University of Iceland but with no results yet published in a peer reviewed journal (Haraldsson et al., 2013).

The primary endpoints of the time & motion trial were the quantification of active healthcare professional (HCP) time and the costs associated with SC administration of trastuzumab compared to the standard IV infusion for patients treated within the PrefHer trial. Additionally, patient infusion chair time and the total time spent in the care unit, for both routes of administration were validated. The results of 24 patient episodes (12 SC, 12 IV) were evaluated. The SC routes lead to a 3-times reduction of the total preparation and administration time, while 4-times less chair-time was required. Per-patient administration this resulted in time saving of 68 minutes and a total cost saving of €143,09 (Table I). For a full course of adjuvant treatment this reflects a cost saving of €2575,62 and time saving of 19 hours and 16 minutes (Table I). According to the authors, these results would mean an impressive cost saving of an estimated 19,2 million euro for UK’s National Health Service (NHS).

In a similarly designed trial from the Iceland Institute of Economics the total patient time spent in hospital, the duration of administration and health care costs were validated. Interestingly, authors attempted to quantify an additional benefit to local insurance system including into the equation a productivity parameter for the patients. This parameter was estimated as the decrease in contribution to gross national income as the result from women having to spend time at day ward unit instead of taking part in some productive market activity. For this calculation authors estimated an employment rate of 0-27,6% for women under treatment with adjuvant trastuzumab. Results were also favouring the arm of SC trastuzumab. In 2012, 65 patients received trastuzumab at the day ward. These patients accounted for 919 visits to the ward, of which 27 were defined as first-time visits and 892 as subsequent visits. Total cost saving in 2012 could have been between 38,400 euro and 45,000 euro. This increased efficiency is also improving the healthcare quality. Results for the two trials are described in Table I.

Additionally in the 2013 European Cancer Congress, the difference of healthcare professional time and patient chair time for trastuzumab IV vs. SC was presented in a short abstract for Denmark, France, Italy and Switzerland (Table II) (De Cock, 2013). In all countries there was time saved for healthcare professional and patients, as far as we are aware this data has not been validated or published.
**Table 1.** — Time and money differences between the two administration forms of trastuzumab.

| Administration IV vs. SC | Time & motion study | Iceland study |
|--------------------------|---------------------|---------------|
| **Time spent in Daycare** | IV: 94.5 min SC: 30.3 min | IV: 170-257 min on 1st visit and 90-177 min on the following visits SC: 16-52 min |
| **“Active chair time”** | IV: 75 min SC: 19.8 min | IV: 90-112 min on 1st visit and 40-62 min on the following visits SC: 3-22 min |
| **Cost of preparation and administration** | IV 185.51 € - HCP time: 168.98 € - Consumables: 16.53 € SC 42.42 € - HCP time: 40.92 € - Consumables: 1.5 € | IV first visit: 62-81 € IV subsequent visits: 42-59 € SC: 1-11 € |
| **Cost saving within unit and pharmacy when given SC** | 143.09 € | 61-70 € for each 1st visit and 41-48 € for subsequent visits |
| **Cost savings of a full course (18 cycles)** | 2575.62 € | Minimum: 758 € Maximum: 886 € |

IV = intravenous; SC = subcutaneous; Min = minutes; £ 1 = € 1.28 (exchange rate of 5 December 2014); € 1 = ISK 161.20 (According to the Iceland Bank the average exchange rate in 2012).

**Discussion**

In recent years, drug development is focusing in alternative ways on anticancer treatment administration, targeting practical aspects and convenience for the patient. Oral anticancer treatment is more popular, while less has been devoted to the potential of SC administration as an alternative. However, recent approvals (trastuzumab, bortezomib, omacetaxine) seem to show a renewed interest in this route of administration. Relative comparative studies with intravenous route of administration showed comparable clinical issues with an advantage for subcutaneous formulations in terms of practicality (Leveque, 2014). From a financial point of view, SC formulations of monoclonal antibodies could lead to lower healthcare costs, but still data from studies are limited, while other factors like the coming arrival of the less expensive IV “biosimilars”, that will reduce the cost of hospitalization, may further complicate the scenery.

The aforementioned trials, focusing on SC trastuzumab’s socio-economical impact, resulted in impressive results benefitting healthcare resources independently of the local healthcare systems, structural organization and financial aspects. However, both trials had several limitations.

In the time & motion trial a major consideration was the ‘pricing’ of HCP time and the related interpretations in cost savings. In fact, reference costs were applied to each observed activity, but HCP time was ‘priced’ using unit costs taken from UK NHS reference costs, using the Personal Social Services Research Unit (PSSRU) (Curtis, 2011). This reference represents an extended and complicated financial analysis of costs related to health care professionals without clear definition of final selected reference values used for the calculation in the study. Additionally it was assumed that the recorded active HCP time corresponded to 100% of the time spent by patient when treated. This assumption declines grossly from reality, since mostly HCPs carry out more parallel activities in a day-care centre.

Furthermore, despite the fact that the authors recognized a potential additional benefit from the increased capacity and number of available appointments within the unit, they did not include the parameter in the potential ‘cost and time’ benefit calculation. An additional two patients could have been treated with SC administration in the time it would take to administer one IV treatment. The benefit from redacted waste of partly used vials of medication, was also not included, since SC dose is standard and not weight-based as IV form. Finally, the calculated treatment times can’t be considered realistic, since the patient population was that of the PreHer study and patients in clinical trial setting are always treated ideally in priority. This observation will undoubtedly lead to an optimist calculation.

The Icelandic study had also some major limitations. The cost interpretation of the used time was based only on the average hourly wage per qualified nurse including the social security...
contributions, as calculated in the Iceland National Statistics Services report of 2012. The precise data for pharmacy personnel were not available and were therefore grossly estimated. In fact, no data existed regarding the average time it took staff at the hospital pharmacy to process orders of trastuzumab. The fact that SC administration required no input from the hospital pharmacy, which would also result in time-savings, were also not calculated. Additionally, the time spent by doctors was not included, since local treatment procedures do not include doctor’s involvement. Furthermore we believe that the inclusion of the “productivity” parameter in final cost calculation would have made it more inaccurate, since it represented a highly fluctuating parameter. Finally it has to be noted that the data presented in this study are not yet published in a peer-reviewed journal.

These limitations, the differences in local treatment practices, the differences in selection procedures and endpoints between the two studies discouraged us from direct comparisons of the results. The complexity in the time to cost interpretation including gross assumptions and extrapolations makes the comparison more complicated. Despite these drawbacks, both trials concluded in a clear benefit for SC trastuzumab with total savings of 2,575,62 euro for a full course in the UK and of 758-886 euro for a full course in Iceland. For Belgium with more then 10,000 breast cancer per year this could mean an estimated saving of 1.4 to 4.6 million euros per year.

It is interesting that in none of these trials the extra benefits from the potential increased efficiency have been calculated, despite mentioned in both. This advantage is clearly defined by the higher capacity and number of available appointments within the unit when SC administration of trastuzumab is applied. The extra time saved from HCPs could also induce quality of care and further improve cost efficiency, since they could be involved in other clinical activities. These points could perfectly fit in a LEAN working oncology day-care unit. In fact, “Lean Oncology”, is a term coined to identify a methodology of care and treatment to cancer patients, consisting on process simplification, streamlining of the organization and routes of drug treatment, detection and elimination of waste (Montesarchio et al., 2012). Its main objective is the centrality of the patient. Thus, the successful incorporation of a simplified and time saving clinical procedure, like SC trastuzumab administration, in a LEAN working oncology environment, could give advantages yet to be validated. The next to be considered in this concept is the self-administration of SC trastuzumab.

Conclusion

Based on the current limited data, a substantial benefit for the healthcare recourses could be assumed. Still the small numbers of patients included, the aforementioned limitations and the differences of local healthcare structure discourage from definitive conclusions. Additionally it has to be noted that the efficacy and safety of SC trastuzumab is currently further investigated (SafeHer/ NCT01566721 study).

For these reasons, we plan a non-interventional, prospective trial to assess economical aspects of the two delivery forms in a LEAN working day-care chemotherapy unit, based on a “slot” formatted agenda of procedures. The goal will be to measure the mean difference in cost of healthcare resources (HCP time, consumables, waste elimination) used in the administration of SC and IV trastuzumab when a LEAN based treatment planning is followed. The validation of potential additional benefits will have a major impact on the healthcare system.

References

Arteaga CL, Sliwkowski MX, Osborne CK et al. Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol. 2011;9:16-32.

Burcombe, R, Chan S, Simcock R et al. Subcutaneous Trastuzumab (Herceptin®): A UK Time and Motion Study in Comparison with Intravenous Formulation for the Treatment of Patients with HER2-Positive Early Breast Cancer. Adv Breast Cancer Res. 2017;2:133-40.
Piccart MJ. Proposed treatment guidelines for HER2-positive metastatic breast cancer in Europe. Ann Oncol. 2001;12(Suppl 1):S89-94.

Piccart-Gebhart MJ, Proctor M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353:1659-72.

Pivot X, Gligorov J, Müller V et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol. 2013;14:962-70.

Pivot X, Gligorov J, Müller V et al. Patients preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study. Ann Oncol. 2014;25:1979-87.

Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365:1273-83.

Vu T, Sliwkowski MX, Claret FX. Personalized drug combinations to overcome trastuzumab resistance in HER2-positive breast cancer. Biochim Biophys Acta. 2014;1846:353-65.

Wynn C, Harvey V, Schwabe C et al. Comparison of subcutaneous and intravenous administration of trastuzumab: A phase I/Ib trial in healthy male volunteers and patients with HER2-positive breast cancer. J Clin Pharmacol. 2013;53:192-201.