Subcutaneous vs Intravenous Trastuzumab/Pertuzumab: A Time and Motion Substudy of a Phase II Trial of Adjuvant Trastuzumab/Pertuzumab for Stage I HER2+ Breast Cancer (ADEPT trial)

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ABSTRACT

PURPOSE The time required for in-clinic drug administration can substantially affect breast cancer patients' quality of life. Subcutaneous (SC) drug administration, as opposed to intravenous (IV), may reduce this time commitment. This study sought to estimate the difference in time burden between IV and SC administration of trastuzumab and pertuzumab (HP).

METHODS We prospectively enrolled a subcohort of patients participating in the ADEPT trial (ClinicalTrials.gov identifier: NCT04569747, investigating adjuvant HP plus endocrine therapy for stage I human epidermal growth factor receptor 2–positive breast cancer) to this single-arm crossover time and motion substudy. Patients received two cycles of IV HP followed by two cycles of SC HP. During each cycle, time points in drug preparation and administration were captured. The primary end point was total patient time in the treatment chair. Additional end points included total patient treatment experience time and total pharmacy workflow time. A sample size of 22 patients was estimated to provide 90.7% power with two-sided alpha .05 to detect a difference of 70 minutes in the primary end point by treatment arm (IV *v* SC).

RESULTS Twenty-two patients were enrolled. The mean total patient time in the treatment chair was 61.8 minutes shorter with SC versus IV HP (22.5 *v* 84.3 minutes; $P < .0001$). The mean total patient treatment experience time (incorporating time spent waiting for treatment initiation and time spent in the treatment chair) was 81.8 minutes shorter for SC administration (96 *v* 177.8 minutes; $P < .0001$). The pharmacy workflow time was 78.2 minutes shorter for SC versus IV formulation (41 *v* 119.2 minutes; $P < .0001$).

CONCLUSION SC administration of HP shortened patient time burden by approximately 1 hour. SC drug administration can facilitate faster workflows for health care professionals and improve patients' breast cancer treatment experience.

ACCOMPANYING CONTENT

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Protocol

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INTRODUCTION

Approximately 15%-20% of all human breast cancer shows amplification of the *ERBB2 oncogene*, which encodes a tyrosine kinase growth factor receptor.[1,2] HER2-positive (HER2+) breast cancer in both the early and metastatic settings is typically treated with a combination of chemotherapy and HER2-directed therapy, including the anti-HER2 monoclonal antibodies trastuzumab and pertuzumab (HP).[3-6]

H and P were both initially developed as intravenous (IV) infusions and are often still administered as such. However, more recently, subcutaneous (SC) trastuzumab and a fixed-

CONTEXT

Key Objective
What is the difference in time burden for patients and health care providers between intravenous (IV) versus subcutaneous (SC) administration of trastuzumab and pertuzumab (HP)?

Knowledge Generated
Patients spent on average 61.8 fewer minutes in the treatment chair with SC administration of trastuzumab/pertuzumab, compared with IV administration. The pharmacy workflow time was 78.2 minutes shorter for the SC formulation.

Relevance
SC administration of HP reduces the amount of time that patients with breast cancer spend in clinic and facilitates faster health care professional workflow.

dose SC combination of HP have been developed and shown to be safe and noninferior to the IV forms.[7,8] Furthermore, more than 90% of patients in the PrefHer study and 85% in the PHranceSCa study preferred SC injection of trastuzumab and fixed-dose HP, respectively, as compared with IV infusion, citing reasons such as reduced clinic time and improved comfort during administration.[9,10] Both time and comfort are important components of a breast cancer patient's overall quality of life. In particular, time-consuming treatments can pose significant psychosocial, financial, and work-related toxicities for patients.[11] A better understanding of the potential time savings of SC administration is important for optimizing quality of life in this patient population, as well as health system efficiency.

In this time and motion (T + M) study, we compared the relative logistical burden between SC and IV administration of HP through the prospective capture of various time points during the treatment process. We sought to compare the amount of time patients spent per treatment encounter, as well as time spent by pharmacists in preparing the treatment, for IV versus SC administration of HP. We hypothesized that the time needed for patient treatment and drug preparation would be lower with SC administration when compared with IV administration.

METHODS

Patient Cohort

We prospectively enrolled a prespecified subcohort of patients participating on the ADEPT trial (ClinicalTrials.gov identifier: NCT04569747) to this T + M substudy. The ADEPT trial is an ongoing single-arm prospective phase II trial of adjuvant SC HP (for 1 year) plus endocrine therapy for patients with hormone receptor–positive and HER2+ stage I (pT1N0 or pT1N1mi) breast cancer. Patients eligible for ADEPT have completed primary breast surgery and are systemic therapy-naïve. Patients who received cycle 1 of loading SC HP at Dana-Farber Cancer Institute, tolerated SC drug administration, and did not plan to discontinue pertuzumab after cycle 1 were eligible for the T + M substudy and enrolled consecutively until the substudy accrual goal was met; accrual to the T + M substudy was mandatory for eligible patients.

Ethics

This study was carried out in accordance with the precepts established by the Declaration of Helsinki. The investigators obtained informed consent from each participant. The study was institutional review board (IRB) approved by the Dana-Farber/Harvard Cancer Center IRB.

T + M Study Procedures

The T + M substudy was a single-arm crossover design in which patients, after receiving cycle 1 of loading SC HP, received two cycles of IV HP (cycles 2 and 3 of therapy overall), followed by two cycles of maintenance dose SC HP (cycles 4 and 5 of therapy overall). Those four treatment cycles (cycles 2-5) were designated for T + M substudy data collection. The method for capturing relevant time points was developed collaboratively with infusion nursing and pharmacy colleagues. During cycles 2-5, time points in the drug preparation and administration process were captured from flowsheets filled out by infusion nurses in real time during the patient encounter (Registered Nurse [RN] flowsheet) or from the electronic medical record (EMR; where data was timestamped in real time as part of routine clinic and pharmacy processes and subsequently aggregated for this analysis). Direct observation was not used. The time points collected as part of the patient experience timeline were patient treatment floor check-in (EMR timestamp), first drug administration start time (EMR timestamp), final drug administration end time (RN flowsheet), and final drug post-treatment observation period end time (RN flowsheet). The time points collected as part of the pharmacy workflow timeline were pharmacist A performs first clinical check and releases HP order (EMR timestamp), pharmacist B performs

second clinical check and verifies order (EMR timestamp), pharmacy drug preparation start (EMR timestamp), pharmacy drug preparation complete (EMR timestamp), drug checked by pharmacist (EMR timestamp), and drug leaving pharmacy (EMR timestamp). Of note, portions of the patient experience timeline and the drug preparation timeline could occur in parallel (ie, initial drug preparation in pharmacy can occur before patient treatment floor check-in).

Study Objectives and End Points

The primary objective of the T + M substudy (a secondary objective of the overall trial protocol) was to estimate the mean time difference between SC versus IV HP in terms of total patient time in the treatment chair (defined as time between first drug administration start time to final drug post-treatment observation period end time). Secondary objectives of the T + M substudy were to estimate the mean difference between SC versus IV HP in terms of overall patient treatment experience time (defined as time between patient treatment room check-in and final drug post-treatment observation period end time), drug administration time (defined as time between first drug administration start time and final drug administration end time), and pharmacy workflow time (defined as time between HP order release by pharmacist and drug leaving pharmacy).

Statistical Methods

We estimated a mean value of 90 minutes for total patient chair time with IV HP cycles and a mean value of 20 minutes total patient time in the treatment chair with SC HP cycles and assumed a standard deviation (SD) of 100 minutes. Using these parameters, a sample size of 22 patients in the T + M substudy cohort was estimated to provide 90.7% power with two-sided alpha .05 to detect a difference of 70 minutes in the T + M primary end point by treatment arm (IV *v* SC drug administration), using an average of the two measurements of each type of administration per patient.

Patients in the T + M substudy who were missing data from a time point affecting the T + M primary end point had that time point replaced with a subsequent time point, such that a total of 88 patient cycle observations (22 patients, with data collected over four treatment cycles per patient) were included in the final analysis. It was prespecified that any patient who discontinued pertuzumab before a T + M treatment cycle would be replaced in the cohort, and any patient who required reloading doses of trastuzumab or pertuzumab during the T + M treatment cycles would have that time point replaced with a subsequent time point, such that only treatment cycles involving maintenance dosing of HP were included in the T + M data set.

For all end points, the average time across both treatment cycles was calculated for each patient, and the overall mean across patients for each of IV and SC administration was computed (with SD). Average times for IV versus SC administration were compared via paired Wilcoxon signed rank tests. Adjustments for multiple comparisons were not included.

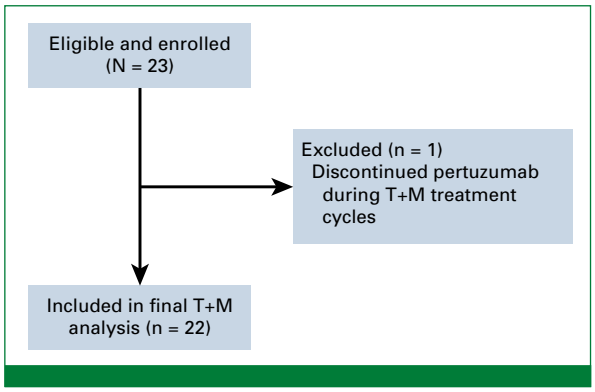

FIG 1. Flow diagram indicating patients eligible for and included in the T + M analysis. T + M, time and motion.

RESULTS

Patient Population

Twenty-three patients were enrolled to the T + M study cohort; one patient discontinued pertuzumab during the T + M treatment cycles and therefore was excluded from all subsequent analyses, for a total of 22 evaluable patients (Fig 1). Patients were a median age of 58 years (range, 42-83 years) and were 96% female, 82% White, 9% Black, and 9% Asian. No patients were of Hispanic ethnicity (Table 1).

T + M Intervals

The timeline of steps in each patient's drug administration experience and in pharmacy drug preparation workflow is diagrammed in Figure 2. Actual time intervals captured for IV versus SC treatment cycles are shown in Table 2. The mean

TABLE 1. Patient Characteristics

Characteristic	Prevalence
Age in years, median (range)	58 (42-83)
<50, No. (%)	4 (18.2)
≥50, No. (%)	18 (81.8)
Sex, No. (%)	
Female	21 (95.5)
Male	1 (4.5)
Race, No. (%)	
White	18 (81.8)
Black	2 (9.1)
Asian	2 (9.1)
Ethnicity, No. (%)	
Non-Hispanic	22 (100.0)

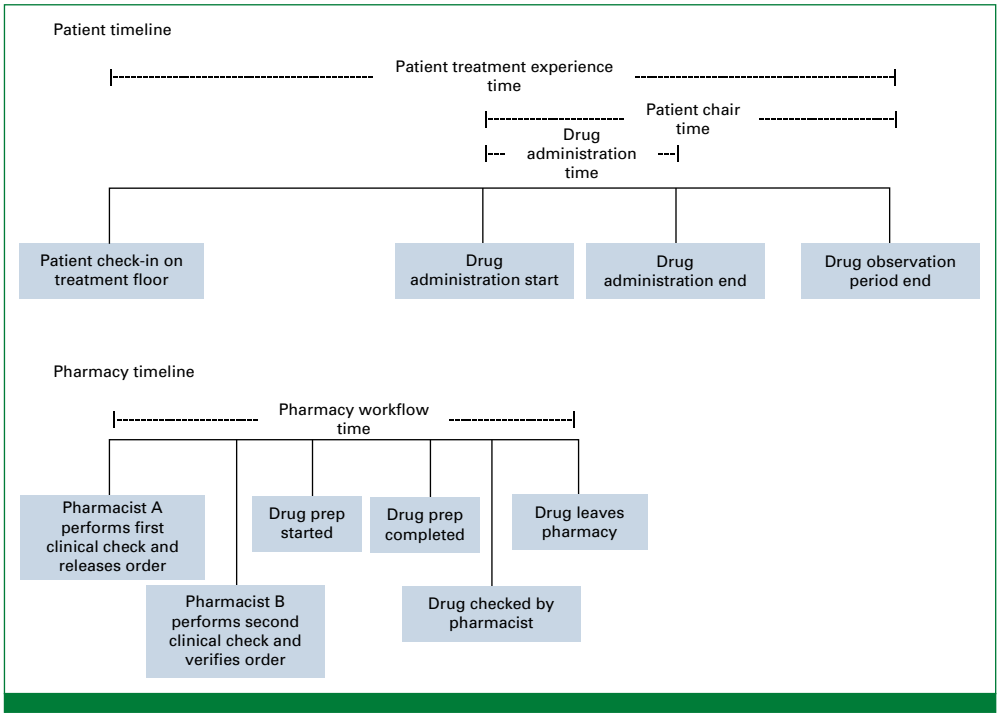

FIG 2. Ordered timeline of patient experience and pharmacy workflow time points captured in this time and motion analysis. The prespecified time intervals of interest are depicted above the timelines.

total patient time in the treatment chair, which combines drug administration time and postadministration observation time, was 84.3 minutes with IV HP and 22.5 minutes with SC HP, for a difference of 61.8 minutes shorter patient chair time in favor of SC administration ($P < .0001$). The mean total drug administration time was 54.2 minutes shorter with SC as opposed to IV drug administration (61.6 minutes with IV HP *v* 7.4 minutes with SC HP; $P < .0001$). The mean total patient treatment experience time, which combines time spent waiting for drug administration to begin and drug administration/observation time, was 81.8 minutes shorter with SC as opposed to IV drug administration (177.8 minutes for IV HP *v* 96 minutes for SC HP; $P < .0001$). Finally, the pharmacy workflow timeline was 78.2 minutes shorter for SC drug preparation (119.2 minutes mean total pharmacy workflow time for IV HP *v* 41 minutes for SC HP; $P < .0001$).

DISCUSSION

In this T + M study, we captured several time points throughout the treatment process with both IV and SC HP. We sought to identify differences in time burden for both patients and health care providers between IV and SC drug administration. Our findings show that SC administration was significantly faster than IV administration across all measured outcomes, including patient time in the treatment chair (primary outcome), as well as pharmacy workflow time, drug administration time, and total patient experience time.

Our findings are consistent with prior T + M literature regarding SC drug administration. The time savings provided by SC injections over IV infusions have been reported for other SC antineoplastic agents, but have not previously been reported for fixed-dose HP.[12,13] Specifically, T + M studies have similarly demonstrated reductions in mean chair time of 230 minutes and 195 minutes for SC daratumumab and rituximab, respectively.[13,14] Previous studies have also shown that most patients prefer SC administration over IV because of the time savings, affirming the importance of time burden as a factor in cancer patients' quality of life.[9,10,15]

The consideration of time spent coordinating, accessing, and receiving care has been conceptualized in the oncology literature as time toxicity.[16] Time toxicity can have far-reaching impacts on all aspects of patients' lives, whether psychological (constant reminders of illness), social (decreased time available to meaningfully engage in relationships), or professional and financial (inability to work).[11] While our reported time savings should be considered within the context of overall trip time, even modestly shorter individual treatment encounters because of SC drug administration, over the prolonged span (at least 12 months) during which patients are on anti-HER2 therapy, can result in a considerable reduction in overall time toxicity. For example, time savings associated with use of SC rituximab over IV rituximab led to an absolute reduction in extrapolated chair time of 3.1-5.5 8-hour days over the first year of treatment.[13] Previous studies show that when patients have to spend less time in cancer

TABLE 2. Time Intervals With IV Versus SC Drug Administration

Time Description (interval measured)	Time Spent, IV Cycles, Mean (SD) in Minutes	Time Spent, SC Cycles, Mean (SD) in Minutes	Mean Difference Between IV and SC Cycles (minutes)	*P*
Total patient time in treatment chair (first drug administration start to final postdrug observation period end)	84.3 (11.9)	22.5 (2.6)	61.8	<.0001
Total drug administration time (first drug administration start to final drug administration end)	61.6 (6.5)	7.4 (2.3)	54.2	.0001
Total drug preparation time (order release by pharmacist to drug leaving pharmacy)	119.2 (35.5)	41 (15.7)	78.2	<.0001
Total patient treatment experience time (treatment room check-in time to final post-drug observation period end)	177.8 (34)	96 (17.5)	81.8	<.0001

Abbreviations: IV, intravenous; SC, subcutaneous; SD, standard deviation.

treatment facilities, they prioritize more time spent at home.[16,17]

An advancement in the field of time toxicity has been the introduction of time toxic days or hospital contact days, defined as days that a patient physically leaves their home to access health care.[18] This concept exposes that modest survival benefits imparted by new treatments may be attenuated by a decrease in quality of life because of increased hospital contact days. Within this framework, medical care provided at a patient's home is less time toxic than traditional hospital-, clinic-, or infusion center-based care. Although SC drug administration in the clinic does not affect time toxic days, notably, SC drug formulations are attractive in that they may facilitate home drug administration. A study exploring home SC HP administration in the United States during the COVID-19 pandemic found that the safety of SC HP at home was consistent with the established HP safety profile.[19] The BELIS study conducted in Belgium and Israel found that home administration of SC trastuzumab was safe and associated with high patient and health care provider satisfaction.[20] These findings have been replicated by a number of other small pilot studies across Europe.[21]

While home administration of SC HP is not yet widespread in the United States, further development of workflows and equipment may allow home administration to become a future standard of care, further helping patients to maximize time at home and minimize disruption during treatment of HER2+ breast cancer. Although this would certainly decrease time toxic days, data are somewhat mixed regarding the cost implications of home SC oncology drug administration. In a micro-costing study in the Netherlands that compared home-based versus hospital-based administration of SC trastuzumab, health care system costs were higher for home-based administration, whereas costs for patient/family were lower, with these differences largely arising because health care professionals took on additional travel expenses to administer drug at home, whereas patients saved on travel costs.[22] If future home drug administration protocols are developed, detailed analysis of the pros and cons at the societal, health care, and patient levels should be considered. Moreover, procedures/equipment to allow self-injection would be helpful, as home nurse administration of at-home agents is complex and costly. In addition to patient-facing advantages, the time savings of SC HP administration may also benefit oncology centers. As our study demonstrates, SC administration of drug translates to less time needed for pharmacy workflows. Although nursing time was not specifically measured in our study, the per-patient nursing time commitment likely decreases in parallel with decreased drug administration time requirements. This is supported by published nursing and health care provider perspectives favoring SC HP and trastuzumab, as well as objective nursing and health care provider time savings reported for SC daratumumab and rituximab.[13,14,21,23] Shorter per-patient time spent in treatment could allow centers to treat more patients in a given day, improving appointment access and increasing throughput. For example, a discrete event simulation model built to estimate the effects of SC daratumumab found that SC daratumumab would allow infusion centers to avoid increases in wait times and wait lists.[24] In turn, increased staff and patient efficiency can lead to cost savings for health care centers: A T + M study in the United Kingdom found cost savings with SC versus IV rituximab, primarily due to reductions in staff costs with SC administration.[25]

The broader pharmacoeconomic conversation about adoption of SC versus IV oncologic therapy is inherently multifaceted and complex, involving payer, provider, patient, and pharmaceutical interests. Some argue that development of IV biosimilars should be prioritized over SC formulations, given that developing SC formulations extends drug patent life and therefore passes greater costs onto health systems, insurers, and patients, for the profit of pharmaceutical companies. An economic simulation model found greater cost-efficiency (from the payer perspective) with an IV trastuzumab biosimilar over SC trastuzumab.[26] However, this sort of analysis does not account for costs to patient and society in terms of patient expense around drug administration (eg, out-of-pocket drug costs which may favor IV biosimilars *v* childcare costs which may favor SC

formulations) and employment disruption. Micro-costing analyses are one tool to better capture multilevel cost data.[27]

Despite the associated time savings and patient preference for SC over IV drug administration, the uptake of SC oncologic drugs is far from universal. The determinants of IV versus SC adoption are multifaceted, interconnected, and vary by country. Infrastructure challenges such as nursing shortages, alongside reimbursement and formulary policies, serve as structural drivers influencing the preference for IV or SC administration. Similarly, physicians' clinical familiarity with different formulations and patients' preferences also significantly affect adoption rates of either route.

Our study has several limitations. We did not capture patient-reported outcomes regarding IV versus SC treatment experience and thus cannot comment on how drug administration method affected patient quality of life. Patient-reported outcomes exploring many different quality-of-life parameters, including experience and satisfaction with SC drug administration throughout the duration of adjuvant therapy, are being recorded for all participants in the ADEPT trial, and will be reported with the overall trial results. Because of the need to capture highly standardized patient flow time points in real time, T + M data were measured only for patients receiving treatment at a single institution (Dana-Farber Cancer Institute) and therefore may not be generalizable to all other treatment centers. Nonetheless, our data set is unique in its rigorous prospective recording of time intervals on a scale of minutes and demonstrates the multilevel time savings possible with SC drug administration.

In summary, we prospectively compared the time burden of IV versus SC HP administration for both patients and health care providers and found that SC HP has a significantly shorter time burden than IV HP across all outcomes measured, with SC administration shortening the patient treatment experience by approximately 1 hour. Increased availability and uptake of SC drug administration may help to improve the breast cancer patient experience and increase oncology center operating efficiency.

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DATA SHARING STATEMENT

Data are available from the corresponding author upon reasonable request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Subcutaneous vs Intravenous Trastuzumab/Pertuzumab: A Time and Motion Substudy of a Phase II Trial of Adjuvant Trastuzumab/Pertuzumab for Stage I HER2+ Breast Cancer (ADEPT trial)

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