

REVIEW

Flexible care in breast cancer

A. Wardley¹, J.-L. Canon², L. Elsten³, C. Peña Murillo⁴, T. Badovinac Crnjevic⁵, J. Fredriksson⁴ & M. Piccart^{6*}

¹NIHR Manchester Clinical Research Facility at The Christie and Division of Cancer Sciences and University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; ²Service d'Oncologie-Hématologie, Site Notre-Dame, Grand Hôpital de Charleroi (GHdC), Charleroi, Belgium; ³Department of Medical Oncology, Amphia Hospital, Breda, The Netherlands; ⁴Global Product Development, Medical Affairs, Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁵PDO - Clinical Science Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁶Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium.



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Treatment of patients with cancer in hospitals or clinics is resource-intensive and imposes a burden on patients. 'Flexible care' is a term that can be used to describe treatment administered outside the oncology ward, oncological outpatient clinic or office-based oncologist setting. Programmes that reduce travel burden by bringing cancer treatment to the patient's home, workplace or closer to the patient's home, in the form of satellite clinics or mobile cancer units, expand treatment capacity and are well received. Clinical trial data show that, compared with intravenous administration, subcutaneous (s.c.) administration of trastuzumab is preferred by patients with breast cancer (BC), saves healthcare professionals' (HCPs) time, reduces drug preparation and administration time and reduces direct and indirect costs. As such, s.c. trastuzumab is well suited to flexible care. The results of a Belgian study (BELIS) show that home administration of s.c. trastuzumab is feasible and preferred by patients with BC. Numerous programmes and pilot studies in Europe show that s.c. trastuzumab can be administered effectively in the patient's home, in primary care settings or local hospitals. Such programmes require planning, training, careful patient selection and technology to link patients, caregivers and specialists in oncology clinics. Once these elements are in place, flexible care offers patients with BC a choice of how treatment may be delivered and lead to improved quality of life, while reducing pressure on HCPs and hospitals. The concept of flexible care is particularly relevant amid the COVID-19 pandemic where guidelines have been developed encouraging remote care.

Key words: trastuzumab, at-home care, remote cancer care, subcutaneous administration, COVID-19

INTRODUCTION

Many anticancer agents are administered by intravenous (i.v.) infusion, which is traditionally provided in a hospital or specialist oncology clinic. This is the only option for many agents; for complex combination regimens it can be inconvenient for patients with cancer who must travel to and from clinics for treatment, often with little flexibility in scheduling.

Treatment of patients with cancer in hospitals or clinics is resource-intensive depending on the type of i.v. access. Some types of access (e.g. port-a-cath) require surgery to implant and are associated with small but significant risks of infection and clot formation. Preparation and administration of i.v. infusions are time-consuming activities. Moreover, long administration and observation periods and the

need for sequential administration places limits on the number of patients who can be treated in a day.

The requirement for treatment in a formal oncology clinic or hospital imposes a societal burden. In general, routine daily activities such as work or childcare responsibilities are disrupted by the need to attend a cancer clinic for treatment. Many patients require caregivers to drive them to appointments; this is a substantial burden when patients must travel long distances for treatment.¹ With respect to breast cancer (BC), treatment causes fatigue, negatively impacts health-related quality of life (HRQoL) and disrupts activities of daily living, including the ability to work and earn income.² The need to arrange transportation and time to travel to a clinic may exacerbate these problems.

In general, patients and their family members find travelling long distances to treatment centres to be inconvenient and time-consuming. Indeed, a high travel burden can lead to delays in the treatment of cancer and is associated with worse prognosis and greater impairment in HRQoL in patients with a wide range of cancer diagnoses.³ A study in patients with lung cancer who travelled long distances to hospital for treatment found that patients perceived

*Correspondence to: Prof. Martine Piccart, Department of Medicine, Jules Bordet Institute, Boulevard de Waterloo 125, B-1000 Brussels, Belgium. Tel: +32-2-541-3206; Fax: +32-2-538-0858
E-mail: martine.piccart@bordet.be (M. Piccart).

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waiting time to be a large burden.⁴ A US study that included patients with breast, colon, cervical or prostate cancer and lymphoma found that some patients may forgo treatment because of transportation barriers such as long distance, lack of access to an automobile or availability of a driver.⁵

Amid the rapidly changing environment of healthcare provision during the global COVID-19 pandemic, the importance of cancer treatment outside the hospital setting is further accentuated. Patients with cancer are at increased risk of complications from COVID-19 and thus alternative strategies for care and risk mitigation are needed.^{6,7}

'Flexible care' is a term that can be used to describe treatment administered outside of the oncology ward, oncological outpatient clinic or office-based oncologist setting; for example, in the patient's home, in primary care settings, community care centres or any other applicable setting.

Bringing cancer treatment to the patient

Programmes that reduce the travel burden by bringing cancer treatment closer to the patient have met with success. Nurse-led mobile chemotherapy units (MCUs) have been providing treatment for patients with a variety of tumour types closer to home in parts of the UK since 2007.⁸ Interviews with patients with a variety of tumour types (e.g. breast, colorectal and others) who received i.v. chemotherapy in an MCU in South West England found that availability of car parking and reduced travel time had a positive effect on quality of life. Moreover, treatment in the MCU was found to be less formal and stressful for the patients, and time spent waiting was perceived to be the most important feature that distinguished treatment in an MCU from a formal outpatient clinic. In addition, patients reported savings in fuel expenditures and companion costs.⁸

Patients referred for treatment to the Oncology Unit of the General Hospital in Piacenza in Northern Italy are offered the opportunity to be treated in an outpatient centre (Casa della Salute) located closer to their homes.⁹ Treatment is administered by a nurse under the supervision of a medical oncologist. Fifty-four patients, 11 of whom (20%) had BC, were treated between July 2016 and July 2017. Among the patient group, the average distance to the outpatient centre was 21 km (versus 82 km to the hospital in Piacenza). The shorter distance resulted in much shorter average travel times for treatment (16 min to the outpatient centre versus 93 min round trip to the hospital) and a very high rate of satisfaction with treatment in the outpatient centre (98.5%).¹⁰ Most patients (65%) who needed a caregiver to reach the Oncology Unit in Piacenza were able to travel independently to the outpatient centre.

Cancer treatment at home

In addition to cancer treatment closer to home, there are programmes that provide cancer care in the patient's home. The concept of a 'hospital-at-home' programme, which

provides care at home for elderly patients with acute conditions, was shown to be feasible and effective.¹⁰ A Cochrane meta-analysis of seven trials evaluating hospital care at home for patients with a variety of conditions concluded that the provision of care at home rather than in hospital was associated with a 38% lower rate of mortality at 6 months.¹¹ An economic analysis of one such 'hospital-at-home' programme showed that costs for patients treated in their own home were lower than for similar patients treated in hospital.¹² More recently, care provided by nurses for patients enrolled in a dedicated oncology 'hospital-at-home' programme in the USA was reported to reduce hospitalisations, emergency department visits and costs, when compared with usual care.¹³

A UK analysis of 'care in the home' suggested that the benefits of treating patients (including patients with cancer, patients with chronic conditions and patients requiring end-of-life care) in their home include better adherence, reablement (i.e. the ability to resume or continue routine daily activities) and improved quality of life, patient activation and financial savings.¹⁴

The concept of home-based treatment for patients with cancer is not new. Several early studies examined the feasibility of administering i.v. regimens at home. For example, a small randomised crossover study conducted in Australia in 1996-1997 showed that patients preferred home-based i.v. chemotherapy compared with hospital-based i.v. chemotherapy.¹⁵ Ten of the 20 patients included in this study had BC. Reported advantages of home-based chemotherapy included elimination of the need to travel to hospital, reduced burden on caregivers and family, ability to carry on with other activities and reduced anxiety. A larger subsequent randomised study in Australia found that patients and their carers were satisfied with domiciliary chemotherapy administered by oncology clinic nurses, with no differences in HRQoL compared with hospital-based chemotherapy.¹⁶ Twenty-six of 40 patients evaluated in this study received treatment for early ($n = 17$) or metastatic ($n = 9$) BC.¹⁶

A Spanish study examined patient satisfaction with i.v. chemotherapy for adjuvant or palliative colorectal cancer delivered at home or in an outpatient cancer clinic.¹⁷ Patient satisfaction was higher among those randomised to receive treatment at home compared with in the clinic, with no differences in use of health services. Of note, there were more voluntary withdrawals in the patient group treated in the clinic compared with the patients treated at home. A study conducted in the UK found that patients with non-small-cell lung cancer (NSCLC) and their carers reported positively on the use of domiciliary gemcitabine and preferred it to in-hospital administration.¹⁸ A total of 249 injections were administered to 24 patients in the study, with only one individual requiring treatment in hospital. Finally, a trial in patients with NSCLC in the UK and Sweden showed that patients preferred home-based administration of i.v. chemotherapy by trained chemotherapy nurses.¹⁹ A majority of physicians were satisfied with distant management of patients in this trial.

In summary, home-based care reduces the need to travel and removes the patient from the hospital environment. The patient receives treatment in the comfort of their own home with family support. This makes it easier to carry on with daily activities before and after receiving treatment. Treatment in the home milieu is particularly relevant under the current circumstances (i.e. the COVID-19 pandemic), especially since the risk of infection is greatest when visiting a hospital. Patients with cancer may be at increased risk of contracting and developing complications of COVID-19,²⁰ particularly if they have comorbid chronic medical conditions.²¹ Many patients are afraid to go to the hospital for cancer care; thus, it is important to protect patients from being exposed to COVID-19.⁶ Alternative treatment strategies that may be considered to reduce the number of in-person visits include switching from infusion to oral therapies, if an equivalent oral formulation is available, or deploying home-care nurses to administer infusion therapies in patients' homes.^{6,7} In the UK, patients have been advised that treatment in the home with subcutaneous (s.c.) therapies is one potential way to reduce hospital visits during the pandemic.²²

Self-administration of parenteral biological agents by the s.c. route is the common mode of delivery in diseases such as diabetes, rheumatoid arthritis, multiple sclerosis and, with the recent approval of emicizumab, haemophilia A.²³ With respect to cancer therapy, s.c. formulations of trastuzumab (Herceptin® SC, F. Hoffmann-La Roche Ltd, Basel, Switzerland), rituximab (MabThera® SC, F. Hoffmann-La Roche Ltd) and bortezomib (Velcade®, Takeda, Cambridge, MA, US) are used clinically. Published data show that when compared with i.v. administration, s.c. administration of rituximab is preferred by patients,^{24,25} reduces chair time,²⁶ reduces time required by healthcare professionals (HCPs),²⁶ results in equivalent HRQoL outcomes²⁵ and is cost-saving.^{25,27} Administration of bortezomib by the s.c. route is better tolerated than i.v. administration,²⁸ is associated with reduced chair time and overall clinic visit time than i.v. administration and is preferred by patients²⁹ and nurses.³⁰ A fixed-dose combination of pertuzumab and trastuzumab for s.c. injection (PH FDC SC; PHESGO™, F. Hoffmann-La Roche Ltd) was approved recently by the US FDA,³¹ and received a positive opinion from the CHMP in the EU.³² An expanded access study that is evaluating home administration of this product has been initiated in the USA.³³ Finally, s.c. formulations of several anti-PD-1 agents [atezolizumab (NCT03735121), nivolumab (NCT03656718) and pembrolizumab (NCT0366559)] are in development. Although not necessarily required for the delivery of cancer care at home or closer to home, the availability of s.c. formulations facilitates such programmes.

The objective of this review is to examine the current status of flexible care in oncology, with a focus on its potential in the treatment of patients with BC.

Patients with HER2-positive BC

Trastuzumab. Trastuzumab (Herceptin®, F. Hoffmann-La Roche Ltd) is a monoclonal antibody directed at human epidermal growth factor receptor 2 (HER2) that is approved

for the treatment of patients with HER2-positive BC. Trastuzumab-containing regimens are the standard of care for patients with early or metastatic HER2-positive BC.³⁴⁻³⁷ In addition to an i.v. formulation, trastuzumab is available in a formulation that contains a permeation enhancer (recombinant human hyaluronidase) that facilitates s.c. administration of higher drug volumes. The drug is administered subcutaneously as a fixed dose in a 5-ml volume over a 2-5-minute period into the thigh.

s.c. trastuzumab was shown to be non-inferior to i.v. trastuzumab with regard to serum trough concentration and pathological complete response (pCR) in the phase III, international, randomised, open-label HannaH study.³⁸ The safety profiles of s.c. and i.v. trastuzumab were similar in HannaH. The final analysis of HannaH showed identical event-free survival rates (65% in both groups) and overall survival rates (84% in both groups) after 6 years' follow-up.³⁹

More data comparing s.c. and i.v. trastuzumab are available from the international, randomised, open-label PrefHer study, in which patient preference was the primary outcome.⁴⁰ Administration of s.c. trastuzumab by hand-held syringe was preferred by 86% of patients, with the most common reasons for s.c. preference being convenience and less pain or discomfort.⁴¹ In addition, a majority of HCPs involved in the trial (73.8%) preferred s.c. administration to i.v. administration (only 1.9% expressed a greater preference for i.v. administration). s.c. trastuzumab was well tolerated in PrefHer with no new safety signals when compared with i.v. trastuzumab. A subsequent analysis of the PrefHer dataset showed similar event-free survival rates in patients who received s.c. trastuzumab and i.v. trastuzumab.⁴²

Collectively, published data show that s.c. administration of trastuzumab is preferred by patients,^{38,41,43-47} saves HCP time and reduces chair time,^{46,48-51} reduces drug preparation and administration costs⁴⁸ and reduces direct and indirect costs⁵⁰⁻⁵² when compared with i.v. administration of trastuzumab.

In addition to data from large clinical trials, there are data from smaller pragmatic studies to show that the advantages of s.c. administration are present when trastuzumab is used in everyday clinical practice. For example, multicentre studies in France (SCuBA) and Spain (Proyecto H-Excelencia) showed that switching the route of administration of trastuzumab (and rituximab) from i.v. to s.c. in hospitals or clinics reduced the mean chair time and allowed for an increase in the number of chemotherapy sessions.^{53,54} A similar study in The Netherlands showed that use of s.c. trastuzumab and rituximab was associated with cost savings compared with i.v. administration of both drugs.⁵⁵

s.c. trastuzumab is well suited for use in flexible care settings, including home administration. The results of the BELIS study show that home administration of s.c. trastuzumab is highly satisfactory from a patient's perspective.⁵⁶ BELIS aimed to evaluate the safety and tolerability of trastuzumab administered in hospital and in the home. A total of 102 Belgian and Israeli patients with HER2-positive early BC who had received six cycles of i.v. trastuzumab in the

neoadjuvant setting received three further doses of i.v. trastuzumab in hospital, followed by three doses of s.c. trastuzumab in hospital and then six doses of s.c. trastuzumab at home.⁵⁶ In this study, trained staff visited patients in their home to administer the drug. The safety profile of s.c. trastuzumab administered in the home was consistent with the known safety profile of trastuzumab and no new safety signals were observed. Among patients who were interviewed about their experiences in BELIS, individuals (20.7%, 18/87) reported that travelling to hospital was a problem due to long travelling time, an inability to travel alone, cost and other difficulties. Before the administration of trastuzumab in the home (cycle 13), 99% (83/84) of patients were satisfied to a large or very large extent with treatments received in hospital (i.v. and s.c.). However, 29.3% (24/82) reported having to wait a long time before being admitted during these visits. Subsequently (cycle 17), all patients (100%, 81/81) were satisfied or very satisfied with home administration of s.c. trastuzumab, and thought treatment at home was beneficial. Only 13.4% of patients were anxious about being treated at home. In addition, all HCPs involved in delivery of home-based treatment in BELIS considered s.c. administration to be quicker and required fewer preparation resources than i.v. administration.

The feasibility of home administration of s.c. trastuzumab in patients with HER2-positive early BC has also been examined in the HOMERUS trial.⁵⁷ In HOMERUS, s.c. trastuzumab monotherapy was administered with the aid of an investigational single-use injection device (SID; not commercially available). The first three cycles were given in the hospital by HCPs and the next three cycles were given at home by trained HCPs or patients (if the patient was deemed competent by the investigator).⁵⁷ This was followed by further cycles of treatment administered either at home or at the hospital according to the patient's choice to complete the entire course of trastuzumab therapy. The primary objective of the study was to assess the safety and tolerability of s.c. trastuzumab. Administration of trastuzumab with an SID was well tolerated in HOMERUS. A total of 7.2% of patients (9/125) stopped trastuzumab therapy due to treatment-emergent adverse events, which compares well with the known safety profile of trastuzumab. Moreover, most patients (96%) chose to continue home administration after cycle 6 of s.c. trastuzumab. HRQoL was also assessed in HOMERUS by Short Form Health Survey questionnaire (SF-36). Improvement in the Physical Component Summary was apparent at cycle 9 (at-home administration) when compared with cycle 3 (in-hospital administration). Scores for the Mental Component Summary and the Mood and Anxiety Symptom subscale were similar for at-home administration and in-hospital administration. HOMERUS also assessed pharmacokinetics of s.c. trastuzumab, and results showed that observed serum trough concentrations were slightly higher than reported pharmacokinetic simulations,⁵⁸ but similar when adjusted for 19% lower estimated clearance in HOMERUS, regardless of location. There was no difference in exposure between home and hospital settings.

Table 1. Examples of European programmes that provide subcutaneous trastuzumab at home or closer to home

Country	Programme name and/or location
France	Santé Service ⁶²
United Kingdom	Homecare/mobile chemotherapy unit, Taunton and Somerset, NHS Foundation Trust ⁶¹ Delivery of s.c. trastuzumab at Maswell Park GP Polyclinic ⁵⁹ Non-i.v. therapy in RMH Satellite at Kingston ⁵⁹ North Cumbria Hospitals NHS Trust ⁶⁰
Spain	Proyecto H-Excelencia ⁵³
Italy	Piacenza General Hospital ⁹ HERHOME, Naples ^{63,64}

i.v. intravenous; s.c., subcutaneous.

Administration of trastuzumab at home or closer to home is becoming a reality with real-world experience acquired in selected European countries such as France, Spain, Italy and the UK (in addition to the studies described above) (Table 1).^{9,53,59-64} Collectively, these programmes show that there are several logistical considerations surrounding home administration of trastuzumab. It is necessary to engage and train personnel to administer trastuzumab in the home. Not all patients are well suited to home administration or will prefer home administration; thus, the decision to administer trastuzumab at home is ultimately taken on the basis of discussions between the patient and their physician. Once staff are trained and patients are selected, transportation must be arranged to enable staff to travel to the patient's home, and to transfer the drug from a hospital pharmacy to a patient's home—all the while maintaining a cold chain. Finally, who will prepare the drug and who will administer the drug must be determined, and processes need to be established for monitoring patients and contacting specialists for advice should it be necessary.

There are several different approaches to addressing these logistical considerations. For example, in the UK, MCUs are used to administer i.v. chemotherapy and support cancer patients in general,⁸ and more specifically to administer s.c. trastuzumab to patients with BC.⁶¹ A pilot programme examined delivery of s.c. trastuzumab at Maswell Park GP polyclinic for patients who would have received all of their treatment at West Middlesex University Hospital (WMUH) previously.⁵⁹ Patients received the first three cycles in WMUH and the remaining 15 cycles at Maswell Park polyclinic. The service was nurse-led and was coordinated via remote access to electronic records at WMUH. Assessment of this pilot programme showed that it had a positive impact on patient experience and made efficient use of NHS resources. In particular, patients had good transport links and access to car parks. At WMUH, the programme freed up capacity and allowed specialist chemotherapy nurses to deliver more complex treatments.⁵⁹

In France, Santé Service provides treatment in the home to patients with BC who are treated with s.c. trastuzumab.⁶² Home treatment is proposed by a referring oncologist and provided by nurses who receive training in the administration of s.c. trastuzumab. A survey of 84 patients who had

received an average of eight s.c. trastuzumab injections showed that home treatment sessions were positive for patients (76% found the sessions to be 'pleasant') and nurses (22% found the sessions 'pleasant' and 67% found them to be 'acceptable'). A majority (95%) of patients said they would recommend the treatment to other patients. Patients described the advantages of home treatment to include no need to travel (49%), rapidity (26%), comfort of injection (11%), practicality and simplicity of treatment, less stress, fatigue and perception of disease and sparing of the veins. A majority of nurses (90%) found the injection procedure to be very easy or rather easy.⁶²

A recently initiated public/private partnership in Italy (HERHOME) designed to deliver s.c. trastuzumab therapy in the patient's home uses a website to coordinate care between oncologists at Naples' Pascale Istituto Nazionale dei Tumori and a third-party provider that provides logistical services and maintains the cold chain.⁶³⁻⁶⁵ Oncologists offered selected patients the opportunity to be treated at home. For patients who elected to be treated in their home, the online platform is used to plan activities and allows communication between a doctor employed by the third party and the patient, including informing the patient that the doctor (and drug) will arrive in 30 min on treatment days (in Italy nurses are not considered qualified to administer drugs in the home). Trastuzumab is prepared and administered in the patient's home, after which the patient is observed by the doctor. The hospital oncologist is available during and after administration to consult should adverse events occur.

Pertuzumab/trastuzumab. Pertuzumab (PERJETA®, F. Hoffmann-La Roche Ltd) and trastuzumab have complementary mechanisms of action and, when administered in combination with chemotherapy, improve outcomes in patients with early or metastatic HER2-positive BC.⁶⁶⁻⁷⁰ Traditionally these drugs have been administered by sequential i.v. infusions with long post-administration observation times. This is inconvenient for patients and the prolonged 'chair time' places fixed limits on the number of patients that can be treated per day in a traditional setting.

s.c. administration of pertuzumab is feasible,⁷¹ which has spurred on the development of PH FDC SC.³¹ The efficacy, safety and pharmacokinetics of PH FDC SC has been compared to separate i.v. infusions of pertuzumab and trastuzumab in a randomised, multicentre, open-label phase III study in patients to HER2-positive invasive BC (FeDeriCa, NCT03493854).^{31,72} The results showed that PH FDC SC was non-inferior to sequential infusions of pertuzumab and trastuzumab with respect to pertuzumab serum trough concentration, that total pCR rates were comparable in the two study arms (59.7% in patients treated with PH FDC SC and 59.5% in patients treated with i.v. pertuzumab plus trastuzumab) and that the overall safety profile of PH FDC SC was similar to i.v. administration of the two drugs.^{31,72}

Patient preference for PH FDC SC has been evaluated in the ongoing multinational, randomised, phase II open-label, crossover PHranceSCa study in patients with HER2-positive early BC.⁷³ Patients who completed neoadjuvant chemotherapy in combination with pertuzumab and trastuzumab i.v. followed by surgery were randomised to receive three doses of PH FDC SC or pertuzumab and trastuzumab i.v. therapy after which they crossed over to the opposite formulation to complete six cycles of treatment. Participants then chose one of the two regimens to complete 18 cycles of anti-HER2 therapy.⁷³ An analysis of data from 160 patients after completing cycle 6 showed that a majority of patients (85% overall) preferred PH FDC SC over pertuzumab plus trastuzumab i.v.⁷³ The most common reason for this preference was that s.c. administration required less time in the clinic. Overall, 88% of patients were 'satisfied' or 'very satisfied' with PH FDC SC (versus 68% of patients with i.v. administration).⁷³

DECRESCENDO is an open-label, phase II study that will examine de-escalation of chemotherapy in patients with HER2-positive early BC. Patients will receive 12 weeks of PH FDC SC plus paclitaxel, after which, those who achieve a pCR will continue with adjuvant PH FDC SC alone for 14 cycles. After completion of neoadjuvant treatment and surgery in the main study, 120 patients who have achieved a pCR will enter a sub-study to assess patient preference for administration of PH FDC SC at home or in hospital. Patients in the sub-study will be randomised to receive three cycles of PH FDC SC in hospital followed by three cycles at home, or to three cycles of PH FDC SC at home followed by three cycles in hospital. Patients may then choose the setting of administration for a further eight cycles of PH FDC SC treatment. The primary endpoint for the sub-study is the proportion of patients choosing to receive treatment outside of the hospital, with quality of life, resource utilisation and HCP experience assessed as secondary endpoints.

An expanded access study in the US has been initiated to evaluate the safety of PH FDC SC administered at home by a home health nurse.³³ The objective of this study is to enable continuity of care during the COVID-19 pandemic for patients with HER2-positive BC. Patients who have completed chemotherapy and are receiving ongoing therapy with pertuzumab plus trastuzumab i.v. will be switched to administration of PH FDC SC at home. Exploratory objectives include evaluating patient preferences for the mode of administration (s.c. or i.v.) and location (home or hospital).

PHARMACOECONOMICS OF S.C. ADMINISTRATION

Several studies have evaluated the financial implications of switching from i.v. to s.c. administration of trastuzumab and rituximab. It should be noted that these studies considered the change in the route of administration only, and not the setting. For this reason, these studies do not reveal the full potential for cost savings associated with flexible care.

A cost minimisation analysis in Singapore demonstrated that s.c. trastuzumab generated significant cost savings compared with i.v. trastuzumab. The key driver of savings was drug cost savings, which amounted to 81%-87% of the total savings.⁷⁴ A study conducted in six hospitals in The Netherlands showed that cost savings can be achieved by switching from i.v. to s.c. administration of trastuzumab and rituximab.⁷⁵ Costs associated with administration of these drugs were consistently lower when administered by the s.c. route. Analyses conducted in Belgian,⁵¹ Danish,⁵² Swedish⁴⁶ and Spanish⁵⁰ oncology clinics show that costs are lower with s.c. when compared with i.v. administration of trastuzumab in patients with HER2-positive BC. French and Spanish analyses showed that s.c. compared with i.v. administration of trastuzumab and rituximab would be associated with an increase in the treatment capacity of oncology clinics.^{53,54} A Canadian analysis estimated that switching from i.v. rituximab to s.c. rituximab would result in significant reductions in systemic chemotherapy suite time and could save up to (\$CAN 2017) \$40 million in drug and administration costs when applied to the entire Canadian market.⁷⁶ The model assumed that uptake of rituximab s.c. would increase from 65% to 80% of cases over a 3-year period.

The DECRESCENDO sub-study (see above) will collect data and measure health economic impact (productivity and cost-effectiveness) in patients with BC treated with PH FDC SC in hospital and at home.

RECOMMENDATIONS FOR THE CARE OF PATIENTS WITH BC DURING THE COVID-19 PANDEMIC

The European Society for Medical Oncology has issued consensus-based recommendations to guide HCPs treating patients with BC during the COVID-19 pandemic.⁷ It is recommended that visits to the hospital be minimised, home-based services be used as much as possible and non-priority outpatient visits be conducted by telemedicine. Patients with the highest risk BCs (triple-negative or HER2-positive early BC) are to be given the highest priority for systemic treatments. Home-based administration of treatment is preferred when possible (i.e. with s.c. trastuzumab). Recommendations are ranked according to priority (high, medium and low) where high priority (tier 1) interventions are those that significantly improve overall survival and/or provide substantial improvement in HRQoL.

Delivery of neoadjuvant and adjuvant chemotherapy in patients with early BC, and delivery of chemotherapy and targeted therapies in patients with metastatic BC, are high priorities for medical oncologists during the pandemic.⁷

SUMMARY AND CONCLUSIONS

Flexible care is an attractive alternative to traditional cancer treatment administered in hospitals or oncology clinics. Flexible care is potentially more convenient for patients, offers resource savings for HCPs and payers, and is particularly well suited to allowing patients to continue scheduled treatment while reducing the need to travel to the hospital.

This alternative has clear advantages over traditional clinic-based care, but is particularly well suited for use during the COVID-19 pandemic.⁷

There is a trend to move care for patients with BC outside hospitals, especially where the evidence of benefit has been established. Data from clinical trials show that s.c. administration of trastuzumab is as safe and effective as i.v. administration, is preferred by patients and reduces direct and indirect costs compared with i.v. administration. The Belgian BELIS trial shows that home administration of s.c. trastuzumab is feasible and preferred by patients. Numerous programmes and pilot studies in several European countries show that there are many ways to deliver treatment closer to home; for example, via MCUs and in GP practices, such as Maswell Park GP polyclinic, in the UK. Treatment in clinics reduces travel time and inconvenience, and increases patient satisfaction. Providing treatment in home or closer to home requires planning, training, careful patient selection and technology to link patients, caregivers and specialists in oncology clinics. Once these elements are in place, flexible care offers patients with BC a choice of how their treatment may be delivered so that they are able to carry on with their daily activities and family and work commitments, while reducing demands on HCPs, hospitals and society.

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Clinical Research Facility at The Christie Hospital, Chair of the NCRI Breast Research Group, Strategy Director for Association of Cancer Physicians, a committee member of the UK Breast Cancer Group and is a committee member of the NHS England Chemotherapy Clinical Reference Group. J-LC reports acting as a consultant or advisor for Pfizer, Roche, Eli Lilly, Daiichi and Novartis; receiving research grants from Amgen and Roche; receiving reimbursement for travel and accommodation expenses from Pfizer and Roche; and acting as a member of a speaker's bureau for Roche. LE reports no other conflicts of interest. CPM reports employment by, and stocks in, F. Hoffmann-La Roche Ltd. TBC reports employment by F. Hoffmann-La Roche Ltd and is a patent holder for PHESGO. JF reports employment by, and stocks in, F. Hoffmann-La Roche Ltd. MP reports grants and personal fees from F. Hoffmann-La Roche Ltd/Genentech (honoraria), Inc., outside the submitted work.

REFERENCES

- Aumann I, Kreis K, Damm K, et al. Treatment-related experiences and preferences of patients with lung cancer: a qualitative analysis. *Health Expect*. 2016;19:1226-1236.
- Mosher CE, Johnson C, Dickler M, et al. Living with metastatic breast cancer: a qualitative analysis of physical, psychological, and social sequelae. *Breast J*. 2013;19:285-292.
- Galipeau N, Klooster B, Krohe M, et al. Understanding key symptoms, side effects, and impacts of HR+/HER2- advanced breast cancer: qualitative study findings. *J Patient Rep Outcomes*. 2019;3:10.
- Ambroggi M, Biasini C, Del Giovane C, et al. Distance as a barrier to cancer diagnosis and treatment: review of the literature. *Oncologist*. 2015;20:1378-1385.
- Guidry JJ, Aday LA, Zhang D, et al. Transportation as a barrier to cancer treatment. *Cancer Pract*. 1997;5:361-366.
- Cinar P, Kubal T, Freifeld A, et al. Safety at the time of the COVID-19 pandemic: how to keep our oncology patients and healthcare workers safe. *J Natl Compr Canc Netw*. 2020;18:504-509.
- de Azambuja E, Trapani D, Loibl S, et al. ESMO management and treatment adapted recommendations in the COVID-19 era: breast cancer. *ESMO Open*. 2020;5:e000793.
- Mitchell T. Patients' experiences of receiving chemotherapy in outpatient clinic and/or onboard a unique nurse-led mobile chemotherapy unit: a qualitative study. *Eur J Cancer Care (Engl)*. 2013;22:430-439.
- Mordenti P, Proietto M, Citterio C, et al. [The treatment of cancer patients near their residence in the territorial structure "Casa della salute": preliminary results in the province of Piacenza (Italy)]. *Recenti Prog Med*. 2018;109:337-341.
- Leff B, Burton L, Mader SL, et al. Hospital at home: feasibility and outcomes of a program to provide hospital-level care at home for acutely ill older patients. *Ann Intern Med*. 2005;143:798-808.
- Shepperd S, Doll H, Angus RM, et al. Avoiding hospital admission through provision of hospital care at home: a systematic review and meta-analysis of individual patient data. *CMAJ*. 2009;180:175-182.
- Cryer L, Shannon SB, Van Amsterdam M, et al. Costs for 'hospital at home' patients were 19 percent lower, with equal or better outcomes compared to similar inpatients. *Health Aff (Millwood)*. 2012;31:1237-1243.
- Mooney K, Titchener K, Haaland B, et al. The oncology hospital at home: health care utilization outcomes from the huntsman at home trial. *J Clin Oncol*. 2020;38. Abstract 7000.
- Featherstone J. Defining the services and measuring their worth. 2015. Available at: https://hah.co.uk/wp-content/uploads/Building_the_case_of_clinical_care_in_the_Home.pdf. Accessed March 23, 2020.
- Rischin D, White MA, Matthews JP, et al. A randomised crossover trial of chemotherapy in the home: patient preferences and cost analysis. *Med J Aust*. 2000;173:125-127.
- King MT, Hall J, Caleo S, et al. Home or hospital? An evaluation of the costs, preferences, and outcomes of domiciliary chemotherapy. *Int J Health Serv*. 2000;30:557-579.
- Borras JM, Sanchez-Hernandez A, Navarro M, et al. Compliance, satisfaction, and quality of life of patients with colorectal cancer receiving home chemotherapy or outpatient treatment: a randomised controlled trial. *BMJ*. 2001;322:826.
- Anderson H, Addington-Hall JM, Peake MD, et al. Domiciliary chemotherapy with gemcitabine is safe and acceptable to advanced non-small-cell lung cancer patients: results of a feasibility study. *Br J Cancer*. 2003;89:2190-2196.
- Lal R, Hillerdal GN, Shah RN, et al. Feasibility of home delivery of pemetrexed in patients with advanced non-squamous non-small-cell lung cancer. *Lung Cancer*. 2015;89:154-160.
- Yu J, Ouyang W, Chua MLK, et al. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. 2020;6:1108-1110.
- Centers for Disease Control and Prevention (CDC). People with certain medical conditions. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html. Accessed July 3, 2020.
- Cancer Research UK. Coronavirus (COVID-19) and chemotherapy, immunotherapy and other cancer drugs. 2020. Available at: <https://www.cancerresearchuk.org/about-cancer/cancer-in-general/coronavirus/cancer-treatment>. Accessed April 26, 2020.
- Bittner B, Richter W, Schmidt J. Subcutaneous administration of biotherapeutics: an overview of current challenges and opportunities. *BioDrugs*. 2018;32:425-440.
- Rummel M, Kim TM, Aversa F, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). *Ann Oncol*. 2017;28:836-842.
- Fargier E, Ranchon F, Huot L, et al. SMABcare study: subcutaneous monoclonal antibody in cancer care: cost-consequence analysis of subcutaneous rituximab in patients with follicular lymphoma. *Ann Hematol*. 2018;97:123-131.
- De Cock E, Kritikou P, Sandoval M, et al. Time savings with rituximab subcutaneous injection versus rituximab intravenous infusion: a time and motion study in eight countries. *PLoS One*. 2016;11:e0157957.
- Mihajlovic J, Bax P, van Breugel E, et al. Microcosting study of rituximab subcutaneous injection versus intravenous infusion. *Clin Ther*. 2017;39:1221-1232.
- Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol*. 2011;12:431-440.
- Barbee MS, Harvey RD, Lonial S, et al. Subcutaneous versus intravenous bortezomib: efficiency practice variables and patient preferences. *Ann Pharmacother*. 2013;47:1136-1142.
- Martin JR, Beegle NL, Zhu Y, et al. Subcutaneous administration of bortezomib: a pilot survey of oncology nurses. *J Adv Pract Oncol*. 2013;6:308-318.
- Food and Drug Administration (FDA). Phesgo® (pertuzumab, trastuzumab, and hyaluronidase-zzxf). Prescribing Information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761170s000lbl.pdf. Accessed September 9, 2020.
- European Medicines Agency (EMA). Phesgo(R): Committee for Medicinal Products for Human Use (CHMP) opinion. 2020. Available at: <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/phesgo>. Accessed December 15, 2020.
- ClinicalTrials.gov. An expanded access, single-arm, multicenter study to provide at home subcutaneous administration of pertuzumab and trastuzumab fixed-dose combination (PH FDC SC) for patients with

- HER2-positive breast cancer during the COVID-19 pandemic. 2020. Available at: <https://clinicaltrials.gov/ct2/show/NCT04395508>. Accessed September 9, 2020.
34. Denduluri N, Somerfield MR, Eisen A, et al. Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology Guideline Adaptation of the Cancer Care Ontario Clinical Practice Guideline. *J Clin Oncol*. 2016;34:2416-2427.
 35. Denduluri N, Chavez-MacGregor M, Telli ML, et al. Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2018;36:2433-2443.
 36. Liedtke C, Jackisch C, Thill M, et al. AGO recommendations for the diagnosis and treatment of patients with early breast cancer: update 2018. *Breast Care (Basel)*. 2018;13:196-208.
 37. Thill M, Liedtke C, Muller V, et al. AGO recommendations for the diagnosis and treatment of patients with advanced and metastatic breast cancer: update 2018. *Breast Care (Basel)*. 2018;13:209-215.
 38. Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre randomised trial. *Lancet Oncol*. 2012;13:869-878.
 39. Jackisch C, Stroyakovskiy D, Pivov X, et al. Subcutaneous vs intravenous trastuzumab for patients with ERBB2-positive early breast cancer: final analysis of the HannaH phase 3 randomized clinical trial. *JAMA Oncol*. 2019;5:e190339.
 40. Pivov 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;14:962-970.
 41. Pivov X, Gligorov J, Müller V, et al. Patient preference for subcutaneous trastuzumab via handheld syringe versus intravenous infusion in HER2-positive early breast cancer: cohort 2 of the PrefHer study. *Cancer Res*. 2013;73(suppl 24):Abstract P4-12-1.
 42. Pivov X, Verma S, Fallowfield L, et al. Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: final analysis of the randomised, two-cohort PrefHer study. *Eur J Cancer*. 2017;86:82-90.
 43. Pivov 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;25:1979-1987.
 44. Fallowfield L, Osborne S, Langridge C, et al. Implications of subcutaneous or intravenous delivery of trastuzumab; further insight from patient interviews in the PrefHer study. *Breast*. 2015;24:166-170.
 45. Jackisch C, Müller V, Dall P, et al. Subcutaneous trastuzumab for HER2-positive breast cancer — evidence and practical experience in 7 German centers. *Geburtshilfe Frauenheilkd*. 2015;75:566-573.
 46. Olofsson S, Norrlid H, Karlsson E, et al. Societal cost of subcutaneous and intravenous trastuzumab for HER2-positive breast cancer — an observational study prospectively recording resource utilization in a Swedish healthcare setting. *Breast*. 2016;29:140-146.
 47. Pivov X, Spano JP, Espie M, et al. Patients' preference of trastuzumab administration (subcutaneous versus intravenous) in HER2-positive metastatic breast cancer: results of the randomised MetaspHer study. *Eur J Cancer*. 2017;82:230-236.
 48. 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. *Cancer Res*. 2013;73(suppl 24):Abstract P4-12-23.
 49. De Cock E, Pivov X, Hauser N, et al. A time and motion study of subcutaneous versus intravenous trastuzumab in patients with HER2-positive early breast cancer. *Cancer Med*. 2016;5:389-397.
 50. Lopez-Vivanco G, Salvador J, Diez R, et al. Cost minimization analysis of treatment with intravenous or subcutaneous trastuzumab in patients with HER2-positive breast cancer in Spain. *Clin Transl Oncol*. 2017;19:1454-1461.
 51. Tjalma WAA, Van den Mooter T, Mertens T, et al. Subcutaneous trastuzumab (Herceptin) versus intravenous trastuzumab for the treatment of patients with HER2-positive breast cancer: a time, motion and cost assessment study in a lean operating day care oncology unit. *Eur J Obstet Gynecol Reprod Biol*. 2018;221:46-51.
 52. Olsen J, Jensen KF, Olesen DS, et al. Costs of subcutaneous and intravenous administration of trastuzumab for patients with HER2-positive breast cancer. *J Comp Eff Res*. 2018;7:411-419.
 53. Abad R, Arenaza A, Bayo J, et al. Impacto en la eficiencia tras la optimización de recursos con la vía subcutánea de trastuzumab y rituximab en los hospitales españoles. "Proyecto H-Excelencia" 6th Tendiendo Puentes (Congreso De Oncología Medica, Hematología y Farmacia Oncohematologica). November 22-24, 2018; Toledo, Spain.
 54. Favier M, Le Goc-Sager F, Vincent-Cantini I, et al. [Medico-economic benefits of subcutaneous formulations of trastuzumab and rituximab in day hospitalisation (SCuBA Study)]. *Bull Cancer*. 2018;105:862-872.
 55. Franken MG, Kanters TA, Coenen JL, et al. Saving healthcare and societal costs by changing the route of administration of oncology drugs. *Value Health*. 2018;21:PCN85.
 56. Denys H, Martinez-Mena CL, Martens MT, et al. Safety and tolerability of subcutaneous trastuzumab at home administration, results of the phase IIIb open-label BELIS study in HER2-positive early breast cancer. *Breast Cancer Res Treat*. 2020;181:97-105.
 57. ClinicalTrials.gov. A study of SC administration of trastuzumab (Herceptin) by SID at home in HER2-Positive EBC participants (HOMERUS). 2019. Available at: <https://clinicaltrials.gov/ct2/show/NCT02040935>. Accessed March 23, 2020.
 58. Quartino AL, Hillenbach C, Li J, et al. Population pharmacokinetic and exposure—response analysis for trastuzumab administered using a subcutaneous "manual syringe" injection or intravenously in women with HER2-positive early breast cancer. *Cancer Chemother Pharmacol*. 2016;77:77-88.
 59. London Cancer Alliance. Care Closer to Home and Medicines Optimisation. 2015.
 60. Roe H. Impact of Switching from Intravenous to Subcutaneous Trastuzumab in the Management of HER2 Positive Breast Cancer. UKONS Annual Conference 2016; November 11-12, 2016; Brighton, UK.
 61. Snell A, Ford M. Assessing the impact of a homecare/mobile chemotherapy unit co-ordinator using subcutaneous herceptin as an example. UKONS Annual Conference 2016. November 11-12, 2016; Brighton, UK.
 62. Pailler C, Chapot T, Softa S, et al. Subcutaneous administration of trastuzumab at home: feedback of patients treated in 2016 by Santé service. *Bull Cancer*. 2018;105:1126-1134.
 63. APM Health Europe. Treating patients at home with subcutaneous injections of Roche's Herceptin Hylecta saves money [press review]. 2020. Available at: <https://www.apmhealthurope.com/freestory/0/67360/treating-patients-at-home-with-subcutaneous-injections-of-roche-s-herceptin-hylecta-saves-money>. Accessed March 17, 2020.
 64. Scienza e Farmaci. Tumore al seno. Al Pascale di Napoli, la terapia arriva al domicilio. La prima volta in Italia. 2020. Available at: http://www.quotidianosanita.it/stampa_articolo.php?articolo_id=80578. Accessed March 17, 2020.
 65. Corriere Del Mezzogiorno. Tumore al seno, il Pascale avvia la terapia domiciliare. Corriere del mezzogiorno. 2020. Available at: https://corrieredelmezzogiorno.corriere.it/napoli/salute/20_gennaio_23/tumore-seno-pascale-avvia-terapia-domiciliare-79a40330-3dfd-11ea-a05f-1ddcfc2c0b77.shtml. Accessed May 6, 2020.
 66. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13:25-32.
 67. Swain SM, Kim S-B, Cortés J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2013;14:461-471.
 68. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372:724-734.

69. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol.* 2016;17:791-800.
70. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med.* 2017;377:122-131.
71. Kirschbrown WP, Wynne C, Kågedal M, et al. Development of a subcutaneous fixed-dose combination of pertuzumab and trastuzumab: results from the phase Ib dose-finding study. *J Clin Pharmacol.* 2019;59:702-716.
72. Tan Antoinette R, Im Seock-Ah, Mattar André, et al. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study. *Lancet Oncol.* 2020.
73. O'Shaughnessy J, Sousa S, Cruz J, et al. Patient (pt) preference for the pertuzumab-trastuzumab fixed-dose combination for subcutaneous use (PH FDC SC) in HER2-positive early breast cancer (EBC): primary analysis of the open-label, randomised crossover PHranceSCa study. *Ann Oncol.* 2020;31(suppl 4):S306-S307.
74. Ghosh W, Lim S, Wong A. Cost-minimisation analysis of subcutaneous versus intravenous trastuzumab for the treatment of early breast cancer and metastatic breast cancer in Singapore. *Value Health.* 2018;21(suppl 2):Abstract PCN55.
75. Franken MG, Kanters TA, Coenen JL, et al. Potential cost savings owing to the route of administration of oncology drugs: a micro-costing study of intravenous and subcutaneous administration of trastuzumab and rituximab in the Netherlands. *Anticancer Drugs.* 2018;29:791-801.
76. Stewart DA, Boudreault JS, Maturi B, et al. Evaluation of subcutaneous rituximab administration on Canadian systemic therapy suites. *Curr Oncol.* 2018;25:300-306.