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ORIGINAL ARTICLE

A randomized trial comparing vascular access strategies for patients receiving chemotherapy with trastuzumab for early-stage breast cancer

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Abstract

Purpose Trastuzumab-based chemotherapy is usually administered through either a peripherally inserted central catheter (PICC) or a totally implanted vascular access device (PORT). As the most effective type of access is unknown, a feasibility trial, prior to conducting a large pragmatic trial, was undertaken.

Methods The trial methodology utilized the integrated consent model incorporating oral consent. Patients receiving trastuzumab-based neo/adjuvant chemotherapy for early-stage breast cancer were randomized to a PICC or PORT insertion. Feasibility was reflected through a combination of endpoints; however, the a priori definition of feasibility was > 25% of patients approached agreed to randomization and > 25% of physicians approached patients. Secondary outcomes included rates of line-associated complications such as thrombotic events requiring anticoagulation, line infections or phlebitis.

Results During the study period, 4/15 (26.7%) medical oncologists approached patients about study participation. Of 59 patients approached, 56 (94.9%) agreed to randomization, 29 (51.8%) were randomized to PICC and 27 (48.2%) to PORT access. Overall, 17.2% (5/29) and 14.8% (4/27) of patients had at least one line-associated complication in the PICC and PORT arms respectively. The study was terminated early due to slow accrual.

Conclusion The study met its feasibility endpoints with respect to patient and physician engagement. However, the slow rate of accrual (56 patients in 2 years) means that conducting a large pragmatic trial would require additional strategies to make such a study possible.

Trial registration ClinicalTrials.gov Identifier: NCT02632435

Keywords Vascular access · Trastuzumab · Chemotherapy

Background

For patients receiving intravenous (IV) treatments for early-stage breast cancer (EBC), several vascular access strategies exist. These include peripheral access, peripherally inserted central catheters (i.e. PICC lines) or a totally implanted vascular access device (i.e. PORT). However, each type of access has its own risks, benefits and associated costs to both the patient and the health care system [1, 2] (Table 1). While most patients receiving intravenous (IV) trastuzumab-based chemotherapy regimens will have either a PICC or PORT, surveys show significant variability in the use of central lines not only with different chemotherapy regimens but also with their use with the same regimen [3, 4].

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Table 1 Overview of peripheral and central venous access devices commonly used for chemotherapy administration [1, 2, 13–19]

	Peripheral IV	PICC line—peripheral inserted central catheter	PORT
Device description	Catheter less than 3 in. in length	Central venous catheter inserted in peripheral vein and tip in SVC	An implanted reservoir placed usually in the chest, attached to a catheter with tip position in SVC.
Insertion	Percutaneous venipuncture into peripheral vein in hand or arm. No radiology guided or interventional radiology Not contraindicated in active infection or neutropenia	By ultrasound guidance, catheter is inserted to large peripheral vein in the arm above the antecubital fossa. Not contraindicated in thrombocytopenia or coagulopathy	Minor surgical procedure by interventional radiology or surgery. May be done at time of other surgery
Potential delay to initiating chemotherapy	No	Yes	Yes
Costs	Device cheap Requires additional chemotherapy nurse time	Specialist required for insertion Device expensive Requires little additional chemotherapy nurse time	Specialist required for insertion Device very expensive Requires additional chemotherapy nurse time
Length of Dwell	Three days	Several weeks or months	Entire duration of therapy.
Maintenance	No maintenance issues Not used for blood draws	Requires weekly maintenance including dressing changes and flushing Should not be used for blood draws PICC may limit physical activities Precautions during bathing to avoid getting dressing wet	Use for blood draws Access requires non-coring needles Monthly flushing when not used routinely
Complications	Insertion discomfort Difficulty locating an adequate vein Phlebitis Vein sclerosis Infection Extravasation and skin infiltration	Inability to advance catheter to SVC Infection Thrombosis Tip malposition Line migration Line occlusion	Infection Thrombosis Migration/malposition Insertion pain Line occlusion
Removal	None	Removal relatively straightforward and easily performed at the chair side.	PORT removal must be performed by either a surgeon or interventional radiology and requires another incision.

Reviewing the literature comparing the risks (e.g. thrombosis and infection rates) and benefits (e.g. improved patient quality of life) of different vascular access strategies is challenging [1, 2, 5, 6]. Factors affecting the type of access chosen can be patient, provider, regimen and institutional related [3, 4, 7]. These limitations are particularly important when making vascular access recommendations for patients receiving trastuzumab-based therapy, as these patients not only require access for 6 months to 1 year of trastuzumab but may also receive different durations of chemotherapy (e.g. 4 infusions with TC vs 16 with AC-weekly paclitaxel). In addition, many modern regimens (e.g. weekly paclitaxel-trastuzumab regimen) no longer include the potentially vesicant anthracyclines.

The variability in practice likely reflects the different risk-benefit assessments by physicians and patients, which provides evidence of clinical equipoise. This has implications for optimal patient care. While determining the optimal vascular access strategy remains an important medical issue for patients, nurses, physicians and society [4], performing such a trial using the traditional clinical trials model would be challenging. Our team has been evaluating innovative trial designs for comparisons of standard of care interventions that are pragmatic, inexpensive and practical [8, 9].

In the current study, we assessed the feasibility of performing a future large pragmatic, multi-centre randomized clinical trial using this novel trial methodology. We therefore compared PICC versus PORT access in patients receiving trastuzumab-based chemotherapy for EBC.

Methods

Study population

Patients with newly diagnosed Her2-positve breast cancer, who had received no prior chemotherapy and were planned to receive neo/adjuvant trastuzumab-based chemotherapy regimen) at the Ottawa Hospital Cancer Centre, Ottawa; the Irving Greenberg Family Cancer Centre, Ottawa; or the Cancer Centre of Southeastern Ontario, Kingston, Ontario, were potentially

eligible. Patients had to be able to give oral consent and were excluded if there was a contraindication to central line placement. The study was approved by the provincial Research Ethics Board (Ontario Research Ethics Board, OCREB) and local REBs. The trial was registered on clinicaltrials.gov [10].

Trial design and randomization

In this multi-centre and unblinded trial, eligible and consented patients were stratified based on anthracycline use or not and randomized before starting chemotherapy using permuted variable blocks of 3 and 6 via a computerized randomization system developed by the Methods Centre in Ottawa. Randomization was to either PICC or PORT insertion. The protocol for central line insertion was as per local institutional policy/standards. PORTs would usually be left in place for the entire duration of both chemotherapy and trastuzumab while PICCs were usually removed at the end of chemotherapy.

Consent process

The ReThinking Clinical Trials (REaCT) Program was developed for comparing standard of care interventions and is outlined elsewhere [8, 9]. The key components include the following: selection of clinically relevant and practical questions, demonstration of clinical equipoise through surveys of knowledge users [3, 4] and completion of systematic reviews [6], simply defined study endpoints, use of an integrated consent model (ICM) incorporating oral consent [11], efficient REB approval [12] and web-based randomization in the clinic. The REaCT process has been successfully used in studies comparing systemic therapies [8]. While we have previously compared peripheral vein with central line access in patients receiving non-trastuzumab containing chemotherapy regimens [7], the current study was designed to demonstrate whether such a methodology would be feasible for performing a future multi-centre trial in patients receiving trastuzumab-based therapy.

Data collection

Outcome data was collected from physicians using an email template sent when the patient returned to clinic after each chemotherapy treatment and through the patient's electronic health record.

Outcomes

Primary outcomes: feasibility

Trial feasibility was evaluated through a combination of endpoints. These included patient engagement (the percentage of patients approached who agreed to randomization) and physician engagement (percentage of medical oncologists who agreed to participate in the trial compared to the percentage who approached patients regarding the trial). Other endpoints that would allow planning for a future larger pragmatic trial included time for local or provincial REB approval and accrual rates (i.e. percentage of patients who receive (neo)adjuvant IV trastuzumab-containing chemotherapy compared to the number of participants who were approached). Physician and patient adherence with randomization allocation (percentage of patients and are randomized who accept their randomization arm) was also evaluated.

Secondary outcomes: clinical

Secondary outcomes included documented line access-associated complications. These complications included rates of infections (line infections or systemic infections including febrile neutropenia); rates of venous thromboembolism (VTE) (e.g. deep vein thrombosis (DVT) or pulmonary embolism (PE)) and other thrombotic events (e.g. phlebitis or a line thrombus); rates of thrombotic events requiring anticoagulation, upper extremity ultrasound testing, extravasation rates, thrombolytic usage and treatment delays related to vascular access; and rates of line discontinuation. This information was collected both from the treating physician's questionnaires collected at each clinic visit and from the patient's electronic health record. Causality and timing of these events were confirmed by the study PI (MC). Data was also collected on the number of patients randomized to a PICC or PORT who subsequently had this device removed and a different one inserted, as well as the rates of imaging tests (e.g. ultrasounds performed after the line was inserted).

Sample size and statistical analysis

The a priori criteria that needed to be met to deem this feasibility trial successful were if > 25% of appropriate patients who were approached about the study and agreed to participate and if > 25% of physicians who agreed to participate in the study did approach patients for the study. If these feasibility endpoints were met, we planned to expand the study to provide appropriately powered data to evaluate access-associated complications. As this was a feasibility study there was no pre-defined sample size, however, it was pragmatically defined as the sample size reached after 1 year of accrual to demonstrate feasibility of accrual. We anticipated that around 100 patients would be entered per study arm. Feasibility outcomes are presented descriptively. For inferential analyses of clinical outcomes, relative risks with 95% CIs were calculated.

Results

The study ran from March 2016 to March 2018. The study consort diagram is shown in Fig. 1. Of 56 patients randomized,

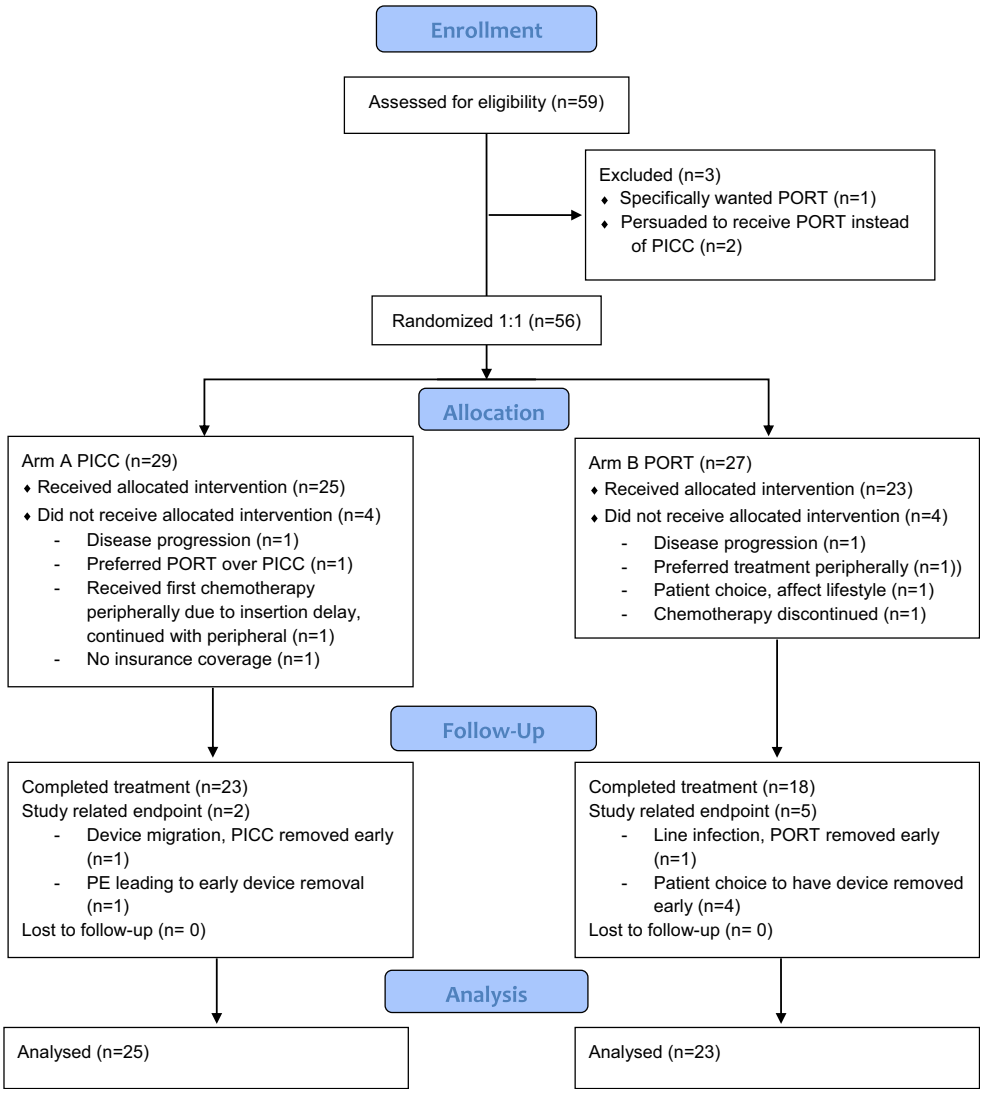

Fig. 1 CONSORT 2010 flow diagram

29 (51.8%) were randomized to PICC and 27 (48.2%) to PORT access. Data were available for analysis for all 56 randomized patients. The baseline characteristics of the randomized patients are shown in Table 2. Median age was 53 years (range 32–84). The most commonly used regimens were FEC-D (21/56, 37.5%), docetaxel/cyclophosphamide (18/56, 32.1%) and docetaxel/carboplatin (11/56 19.6%).

For patients randomized to the PICC arm, a line was actually inserted in 86.2% (25/29) of patients and the line was inserted in the ipsilateral arm to surgery in 3/25 (12%) and the contralateral arm in 22/25 (88%) of patients. For the patients randomized to the PORT arm, a line was actually inserted in 85.2% (23/27) and the line was inserted in the contralateral arm in all 23 patients. The number of days between date of randomization and date of line insertion was 8 (2–40) for PICCs and 8 (1–50) for PORTs, with 4 PICC patients and 2 PORT patients having their first cycle of chemotherapy through peripheral vein and their central line inserted before their second cycle of chemotherapy. Two patients in the PORT arm had 2 cycles of chemotherapy through peripheral vein and their central line inserted prior to their third cycle of chemotherapy. One additional patient had her first cycle administered peripherally, but following chemotherapy-associated complications, chemotherapy was discontinued before a PORT could be inserted. One patient in the PICC arm had their first cycle of chemotherapy and decided they would like the rest of treatment given peripherally, and therefore, the device was never inserted.

Primary outcome measures: feasibility

Patient engagement

Of the 59 potentially eligible patients who were approached for the study at the 2 study sites, 56/59 (94.9%) agreed to randomization. Of the 3 approached patients, the reasons given for not agreeing to enter the study were as follows: persuaded to have a PORT instead ($n = 2$) and preferred a PORT over a PICC line ($n = 1$).

Table 2 Baseline demographics for randomized participants

	PICC *n* = 29	PORT *n* = 27*	Total *N* = 56
Age median	52	54	53
(Range)	(32–84)	(34–82)	(32–84)
Stage, *n* (%)			
1	8 (27.6%)	4 (14.8%)	12 (21.4%)
2	15 (51.7%)	16 (59.3%)	31 (55.4%)
3	5 (17.2%)	7 (25.9%)	12 (21.4%)
Chemotherapy regimen, *n* (%)			
TC-H	9 (31%)	9 (33.3%)	18 (32.1%)
FEC-DH	12 (41.4%)	9 (33.3%)	21 (37.5%)
DD AC-paclitaxel	1 (3.4%)	1 (3.7%)	2 (3.6%)
TCH	6 (20.7%)	5 (18.5%)	11 (19.6%)
PACL W	0 (0%)	2 (7.4%)	2 (3.6%)
**			
Days from randomization to line insertion: *n* (range)	8 (2–40)	8 (1–50)	8 (1–50)
Site of line insertion, *n* (%)			
Ipsilateral to surgery	3 (10.3%)	0 (0%)	3 (5.4%)
Contralateral to surgery	22 (75.9%)	23 (85.2%)	45 (80.4%)
No line inserted	4 (13.8%)	4 (14.8%)	8 (14.2%)

TC-H (taxotere/cyclophosphamide ×4, trastuzumab 3-weekly for 1 year)

FEC-DH (3-weeky FEC ×3, docetaxel ×3, trastuzumab 3-weekly for 1 year)

DD-AC-P (dose-dense AC-paclitaxel….)

TCH (3-weekly docetaxel/carboplatin/trastuzumab ×6 then trastuzumab 3-weekly to 1 year)

PACL W (1-weekly paclitaxel × 12, trastuzumab 3-weekly for 1 year)

*This includes 1 patient who had cycle 1 through a peripheral vein then stopped chemotherapy before a device could be inserted

**Two participants did not have chemotherapy

Physician engagement

Of 15 physicians who initially agreed to participate in the study, 4 (26.7%) approached patients regarding the trial (3/9 in Ottawa and 1/6 in Kingston). Given the low rate of physician engagement, informal enquiries were made to assess whether strategies could be implementated to improve accrual. It was clear repeated emails to the group and presentation at monthly research rounds did not raise accrual. It was felt that despite the findings of the previous survey that individual physicians did not feel there was a lack of equipoise about line use. In addition, the one patient approached at the Kingston site, the investigator noted that nursing staff persuaded them to have a PORT and so they did not enter the study.

Time for local or provincial research ethics approval

The regulatory aspects of opening a REaCT trial are outlined elsewhere [8]. The Ottawa and Kingston centres are in the province of Ontario; the protocol was submitted to the Ontario Cancer Research Ethics Board (OCREB) first. OCREB approval took 2 months. Following provincial approval, the protocol requites approval at each study site; the individual sites had to then complete contracts and have site initiation visits. Thus, the time from initial REB submission to study opening was 4 months at the Ottawa Hospital and 5 months at Kingston General Hospital.

Accrual rates

Data on the number of patients receiving trastuzumab-containing chemotherapy from the time of study opening until closure was only available for the Ottawa site. From March 2, 2016 to April 11, 2018, 339 patients received a trastuzumab-containing neo/adjuvant chemotherapy regimen at the Ottawa site. Of the potentially eligible patients, 58/339 (17.1%) of these patients were approached to participate at the Ottawa site. As the resulting rate of accrual was slower than anticipated with 56 patients accrued over 24 months, the decision was made to close the trial after 56 patients were enrolled.

Patient/physician adherence to randomization allocation

Of the 29 patients randomized to the PICC arm, 4 (13.8%) patients declined their randomization arm due to disease progression ($n = 1$), preferred a PORT instead ($n = 1$), had one cycle of chemotherapy without the PICC as they were awaiting device insertion, and then decided not to have a line inserted ($n = 1$) and did not have OHIP ($n = 1$). Of 27 patients randomized to the PORT arm, 4 (14.8%) patients declined their randomization arm. The reasons for declining their study arm were as follows: disease progression ($n = 1$), declined PORT (due to lifestyle [$n = 1$] and no reason provided [$n = 1$]) and preferred peripheral access after they had one cycle of chemotherapy without a PORT as they awaited PORT insertion and decided not to have the device inserted ($n = 1$). All physicians adhered to their patient's allocated study arm.

Secondary endpoints

Access-associated complications

For access-associated complications, the results are presented by the number of cycles of chemotherapy and trastuzumab administered. The rates of thrombotic complications requiring anticoagulation in the PICC vs PORT groups with risk difference (RD) (95% CI) were as follows: [6 (1.2%) vs 2 (0.43%), RD 0.79 (− 0.38, 1.97)] (Table 3). The thrombotic events were 2 DVTs, 2 PEs and 2 line thromboses in the PICC arm and 2 line thromboses in the PORT arm. Other complications in the PICC vs PORT groups with risk difference (RD) (95% CI) included line infections [0 (0%) vs 2 (0.43%), RD − 0.29 (− 2.02, 1.44)] and phlebitis [0 (0%) vs 1 (0.21%), RD 0.58 (− 0.67, 1.83)] in the PICC versus PORT groups respectively (Table 3). There were no extravasations in either the PICC or the PORT groups. Overall, 17.2% (5/29) and 14.8% (4/27) of patients had at least one of these complications in the PICC and PORT access arms respectively.

The rates of additional imaging (beyond routine chest X-rays for checking the position of PICCs immediately after insertion) included upper extremity ultrasounds [13 (2.6%) vs 6 (1.3%) RD 1.98 (0.03, 3.92)] in the PICC vs PORT groups respectively (Table 3). In the PICC group, the reported reasons for ordering these ultrasounds were; chest pain and SOB ($n = 1$ confirmed PE), swollen arm ($n = 1$ confirmed DVT, $n = 1$ confirmed PE, $n = 1$ confirmed line thrombus and $n = 2$ no clot viewed), check previous clot ($n = 1$ DVT confirmed and $n = 3$ no new clot), rule out clot ($n = 1$ line thrombus confirmed and $n = 1$ no clot viewed) and to rule out a seroma ($n = 1$ no clot viewed). In the PORT group, the reported reasons were red swollen area around PORT ($n = 1$ confirmed line thrombus), to check previous clot ($n = 2$ no clot), fever ($n = 1$ no clot) and check for clot ($n = 1$ confirmed phlebitis and $n = 1$ confirmed line thrombus). Additional chest X-rays were performed in [14 (2.9%) vs 17 (3.6%), RD 0.03 (− 2.45, 2.51)] in the PICC vs PORT groups, respectively. For the PICC patients, chest X-rays were performed to reposition a PICC line after PICC migration ($n = 2$), confirm line position for a patient who had a second PICC line inserted after having first one migrate out ($n = 1$) and to rule out chest infections when patients went to the ER or were hospitalized ($n = 1$ pneumonitis discovered and $n = 10$ nothing discovered). In the PORT patient group, chest X-rays were performed to rule out chest infections when patients were seen in the ER or hospitalized ($n = 1$ opacities viewed on lungs and $n = 16$ nothing discovered).

The consequences of complications in the PICC group included PICC removal (3 patients 10.3%) due to a device migration ($n = 1$), pulmonary embolism ($n = 1$) and early removal request by patient ($n = 1$). Complication consequences for the PORT group included PORT removal (5 patients, 18.5%) due to a line infection ($n = 1$) and patient choice before treatment was completed ($n = 4$). When evaluated by the total number of cycles of chemotherapy, PICC migration complicated 10 cycles (1%), while Cathflo was required in 2 (0.41%) cycles in PICC patients and 1 (0.21%) of cycles in PORT patients.

Discussion

Despite the widespread use of trastuzumab-based chemotherapy in patients with early-stage breast cancer, the optimal type of vascular access remains unknown. Each has its own advantages and disadvantages (Table 1), and the paucity of high quality evidence to guide practice is a result of the lack of definitive trials in this setting [6, 13]. Thus, in clinical practice, it appears that the choice of type of vascular access strategy used is mainly based on physician choice and less so on patient preference [3, 4]. In this setting of clinical equipoise, a clinic trial is needed to identify optimal vascular access strategies. However, performing such a trial will be challenging for a number of reasons including financial, patient and physician-related factors; we therefore decided to evaluate the feasibility of a novel trial methodology that has previously been effective in comparing standard of care pharmaceutical interventions to be used in a pragmatic and relatively inexpensive manner for comparing two standard of care non-pharmacologic interventions (i.e. PICC with PORT).

This is the first prospective trial we are aware of that has directly compared types of lines in patients receiving trastuzumab-based chemotherapy. Unfortunately, despite the majority of patients who were approached about the trial being willing to participate, the feasibility of actually performing the trial was limited as only 4/15 (26.7%) physicians, who initially agreed to participate in the study, actually approached their

Table 3 Study outcome data presented by number of cycles of chemotherapy administered

	Total	PICC *n* (%)	PORT *n* (%)	Risk difference (95% CI)	*P* value
Number of chemotherapy cycles administered	959	491 (51.2%)	468 (48.8%)		
Venous thromboembolism (VTE)	9 (0.94%)	6 (1.22%)	3 (0.64%)	0.58 (− 0.67, 1.83)	0.3541
Type of VTE*					
DVT	2 (0.21%)	2 (0.41%)	0 (0%)		
PE	2 (0.21%)	2 (0.41%)	0 (0%)		
Other thrombotic events	5 (0.52%)	2 (0.41%)	3 (0.64%)		
Type of other TE events:					
Line thrombus	4 (0.42%)	2 (0.41%)	2 (0.43%)		
Phlebitis	1 (0.1%)	0 (0%)	1 (0.21%)		
Thrombotic events requiring anticoagulation (total)	8 (0.83%)	6 (1.22%)	2 (0.43%)	0.79 (− 0.38, 1.97)	0.1792
Infections (total)	17 (1.77%)	8 (1.63%)	9 (1.92%)	− 0.29 (− 2.02, 1.44)	0.7346
Type of infection:					
Line infections	2 (0.21%)	0 (0%)	2 (0.43%)		
Skin infections	6 (0.63%)	5 (1.02%)	1 (0.21%)		
FN or sepsis	3 (0.31%)	2 (0.41%)	1 (0.21%)		
Other	6 (0.63%)	1 (0.2%)	5 (1.07%)		
Upper limb/lower limb ultrasound for potential VTE:				1.98 (0.03, 3.92)	0.0465
Yes	22 (2.29%)	16 (3.26%)	6 (1.28%)		
Upper limb	19 (1.98%)	13 (2.65%)	6 (1.28%)		
Lower limb	3 (0.31%)	3 (0.61%)	0 (0%)		
Additional chest X-rays performed**	35 (3.65%)	18 (3.67%)	17 (3.63%)	0.03 (− 2.45, 2.51)	0.9784
Reason for chest X-ray:					
After insertion to check line position	5 (0.52%)	5 (1.02%)	0 (0%)		
Subsequently to evaluate line migration	2 (0.21%)	2 (0.41%)	0 (0%)		
Other reason+	28 (2.92%)	11 (2.24%)	17 (3.63%)		
Emergency room visit:	49 (5.11%)	25 (5.1%)	21 (4.49%)	0.6 (− 2.23, 3.44)	0.6706
Emergency room visit:					
Related to treatment	9 (0.94%)	6 (1.22%)	3 (0.64%)		
Unrelated to treatment	37 (3.86%)	19 (3.87%)	18 (3.85%)		
Hospitalization:	8 (0.83%)	5 (1.02%)	6 (1.28%)	0.38	0.5232
Number of days hospitalized (range)	4 (1–6)	4 (1–6)	3 (2–3)	(− 0.8, 1.56)	
Hospitalization reason:					
FN	3 (0.31%)	2 (0.41%)	1 (0.21%)		
Infection	1 (0.1%)	0 (0%)	1 (0.21%)		
Other	4 (0.42%)	3 (0.61%)	1 (0.21%)		
Line accessed:	78 (8.13%)	40 (8.15%)	38 (8.12%)	0.03 (− 3.67, 3.73)	0.9884
Line access reason:					
Blood draw	20 (2.09%)	5 (1.02%)	15 (3.21%)		
Line flushing	21 (2.19%)	18 (3.67%)	3 (0.64%)		
Cathflo	3 (0.31%)	2 (0.41%)	1 (0.21%)		
Transfusion	2 (0.21%)	0 (0%)	2 (0.43%)		
Device migration	10 (1.04%)	10 (2.04%)	0 (0%)		
Device repositioning	1 (0.1%)	1 (0.2%)	0 (0%)		
Line replaced:	1 (0.1%)	1 (0.2%)	0 (0%)	0.2	1

Table 3 (continued)

	Total	PICC *n* (%)	PORT *n* (%)	Risk difference (95% CI)	*P* value
				(− 0.002, 0.006)	
Line replaced:					
PICC to PICC	1 (0.1%)	1 (0.2%)	0 (0%)		
PICC to PORT	0 (0%)	0 (0%)	0 (0%)		
PORT to PORT	0 (0%)	0 (0%)	0 (0%)		
PORT to PICC	0 (0%)	0 (0%)	0 (0%)		
Device removed early:	8 (0.83%)	3 (0.61%)	5 (1.07%)	− 0.46 (− 1.65, 0.74)	0.4449
Reason (if stated):					
Patient request	5 (0.52%)	1 (0.2%)	4 (0.85%)		
Blood clot	1 (0.1%)	1 (0.2%)	0 (0%)		
Line infection	1 (0.1%)	0 (0%)	1 (0.21%)		
Device migration	1 (0.1%)	1 0.2%)	0 (0%)		

*Patients can have more than one complication

**This is for patients having CXR beyond standard of care (i.e., for assessment of line position immediately after line insertion)

[+] Other reasons included: rule out pneumonia, check for cardiopulmonary disease: venous thromboembolism (VTE), include deep vein thrombosis (DVT) and pulmonary embolism (PE), thromboembolic (TE), febrile Neutropenia (FN)

patients. Even with extensive efforts to increase accrual, and the findings of a physician survey showing interest in the trial, this accrual did not improve and the trial was closed.

The study did provide important prospective data on line complications. Rates of complications thrombotic events (6 (1.2%) vs 3 (0.64%) for PICC and PORT respectively, compared with 5–7% vs 6–8% in the literature, and infections (8 (1.6%) vs 9 (1.9%) compared with 6–10% vs 6–10% in the literature [1, 2, 13–19]. Line insertion was in the ipsilateral contralateral arm to surgery in 3/49 (6.1%) and 46/49 (93.9%) of cases respectively. Number of patients randomized to PICC who subsequently had a PORT inserted was low, 1 (3.4%) patient decided they wanted PORT instead of a PICC.

There are acknowledged limitations with the current study. The study was small and performed at 2 cancer centres limiting its generalizability. This generalizability includes adherence to "best practice" with respect to central line care [20, 21] for aspects related to avoidance of central venous catheters to routinely draw blood samples, rates of routine flush and check for blood return and chemotherapy nurse education on vascular access devices. There may indeed be patients who were informed of the lower risk of complications with peripheral venous access rather than central line access who would choose to start their treatment peripherally and then assess the need for a central line later [7].

Despite the simplicity of the REaCT process and the use of integrated consent and the lack of requirement for additional study visits, if this important question for patients is to be answered, alternative trial designs are needed. Future studies will also need to take into account patient quality of life as well as larger numbers of patients to get a more accurate assessment of complication rates.

In conclusion, while reliable central vascular access may improve the patient experience by reducing the number of extra peripheral IV attempts, reducing the risk of extravasation, and reducing long term damage to the intima of the vein [13–15], these benefits have not been shown in appropriately designed prospective trials. This is particularly true as we increasingly move away from anthracycline-containing chemotherapy regimens [22]. This is important as lines are associated with higher initial costs, delayed beginning of systemic therapy and a broad range of complications. Optimizing the type of IV access may not only reduce variability in patient care and potentially offer cost savings but also improve patient comfort and acceptability. In the current study, we have failed to demonstrate the feasibility of our novel trials methodology. In addition, the incidence of toxicities reported in our study also means that for a future study to definitively determine optimal IV access however given the generally low level of physician engagement, performing such a trial may be challenging. More trials are clearly needed.

Funding information Funding of this study was through the Rethinking Clinical Trials (REaCT program).

Compliance with ethical standards

We declare that this study complies with ethical standards in Canada. The study was approved by the provincial Research Ethics Board (Ontario Research Ethics Board, OCREB) and local REBs.

Conflict of interest Dr. Awan reports participating in the Novartis Canada Advisory Board on the use of Ribociclib. Dr. Hutton reports personal fees from Cornerstone Research, outside the submitted work. The remaining authors declare that they have no conflicts of interest

(Clemons, Stober, Kehoe, Bedard, MacDonald, Brunet, Saunders, Vandermeer, Mazzarello, Basulaiman, Robinson, Mallick, and Fergusson).

Research involving human participants The study was approved by the appropriate institutional research ethics committees and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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