Will priming intravenous administration sets with monoclonal antibodies reduce chair time in the outpatient setting?

The Priming Practice Study

Investigators & affiliations

Principal Investigators,

Francesca Boyte	Registered Nurse, ODTU
Dr Nicole Gavin	Nurse Researcher, Cancer Care Services

Associate investigators/collaborators,

Michael Smith	Nursing Director, Cancer Care Services
Therese Hayes	Nurse Unit Manager, ODTU & OPU
Marianne Fenton	Associate Nurse Unit Manager, ODTU & OPU
Grant Partridge	Pharmacist, Cancer Care Services
Amanda Sutherland	Quality & Safety Officer, Cancer Care Services
Emily Egan	Nurse Educator, Cancer Care Services
Dr Glen Kennedy	Executive Director, Cancer Care Services
Dr Melissa Eastgate	Medical Oncologist, Cancer Care Services
Lee Jones	Statistician, Queensland University of Technology
Dr Elise Button	Research Fellow, Queensland University of Technology

Investigation site

Royal Brisbane & Women's Hospital

Contents

SYNOPSIS

BACKGROUND	The Oncology Day Therapy Unit (ODTU) provides on average 2000 occasions of service per month or averaging 80 treatments per day. The ODTU provides care for people receiving treatment for haematological and oncological malignancies, apheresis, haemophilia and cytotoxic treatments.
AIM	The aim of this study is to determine whether priming intravenous administration sets with monoclonal antibodies will reduce chair time in the outpatient setting.
PRIMARY OUTCOME	Evaluating whether priming an intravenous administration set with monoclonal antibodies will reduce chair time.
SECONDARY OUTCOME	To evaluate whether priming an intravenous administration set with monoclonal antibodies will reduce the incidence of hypersensitivity reaction, including, time of onset to hypersensitivity reaction, incidence of medical emergencies, admissions to hospital and any delays or reductions in treatment regimes.
DESIGN	The randomised controlled trial is a two-group design to assess priming intravenous administration sets with monoclonal antibodies, *(Intervention Group)* against not priming the administration sets *(control group)* and comparing the chair time.
POPULATION	All cancer patients who meet the following inclusion criteria: 1) 18 years or older 2) Patients attending the Oncology Day Therapy Unit or Oncology Procedure Unit at the RBWH 3) Are being treated with the monoclonal antibodies: Pembrolizumab, Nivolumab, Daratumumab and Obinutuzumab 4) Any cycle of treatment
STUDY TREATMENTS	Patients will commence their treatment regimen of a monoclonal antibody via the control or intervention method. Patients in the control group will commence the monoclonal antibody without a drug primed administration set and patients in the intervention group will commence the monoclonal antibody with a drug primed administration once connected to the IV line allowing for incremental exposure to the drug.
ASSESSMENTS	Primary outcome: chair time will be assessed as time infusion commenced until time infusion completed. Secondary outcomes will be collected from the patient chart and hospital documentation.
STATISTICAL CONSIDERATIONS	A sample size of 128 has been determined. We aim to recruit this sample over 10-12 weeks.

BACKGROUND

The Oncology Day Therapy Unit (ODTU) consists of 22 chair/beds, one isolation room (2 chairs) and 4 chair/beds for apheresis. The oncology procedure Unit (OPU) consists of 7 beds and a Bone Marrow Aspirate procedure room, as well as a blood collection room. ODTU provides on average 2000 occasions of service per month or averaging 80 treatments per day. The ODTU provides care for people receiving treatment for haematological and oncological malignancies, apheresis, haemophilia and cytotoxic treatments. OPU provides on average 1100 occasions of services per month. OPU provides care for people receiving immunotherapy treatment for haematological and oncological malignancies, supportive treatments, blood collections or bone marrow aspirates. By decreasing chair time for patients attending ODTU or OPU, allows for improved patient flow, decreased wait times and increased patient satisfaction. Gjola, Campos, Olier-pino and Fernandez explain that there is a link between patient wait times in a chemotherapy unit and patient dissatisfaction which 'can influence a patient's perception of service quality. These observations can adversely affect patient compliance (2015, P 95).

Targeted therapy stops the action of molecules that can be the key to the growth of cancer cells. There are two main types of targeted therapy, including, small molecule drugs and monoclonal antibodies. Monoclonal Antibodies are a group of medications that harness the body's own immune system to attack cancer cells (eviQ 3460, 2019). Many monoclonal antibodies have the potential for infusion reactions (Vogel, 2010). Infusion reactions are typically mild to moderate intensity and can develop immediately on exposure to the monoclonal antibody or during the infusion (Gobel, 2007). The infusion reactions can have a hypersensitivity basis in which the molecular structure or component of the monoclonal antibody formulation is recognized as an antigen by the immune system (Chung, 2008). Reactions are graded using the Common terminology Criteria for Adverse Events (CTCAE). Mild to moderate infusion reactions (i.e. CTCAE grades 1 and 2 and infusion reactions that do not involve symptoms of anaphylaxis) are the most commonly encountered reactions (EVIQ 1831, 2020). Infusion reactions are most commonly associated with rigors, fever, nausea, headaches, skin rash, pruritus or asthenia however infusion reactions can also present with various signs and symptoms of severe hypersensitivity reaction that can be characterised by

anaphylaxis, acute onset of hypotension or hypertension, bronchospasm, wheezing, transient flushing, urticaria or cardiac arrest

(Chung, 2008). Severe hypersensitivity reactions can lead to hospital admissions, delays in treatments and dose reductions leading to poor patient outcomes.

Priming Intravenous lines (IV) with the drug allows for an incremental exposure to the monoclonal antibody. When a monoclonal antibody is not primed with the drug, patients can be receiving only diluent for a period before being exposed to the monoclonal antibody, leading to increased time in the chair, impacting on patient flow through the outpatient setting. This leads to the delay of other patients and decreased patient satisfaction. When a patient is receiving diluent for a period, they may already have reached the 2nd or 3rd increment before being exposed to the monoclonal antibody. This does not align with safe medication practice as the patient may not begin to receive the medication at the correct rate. This can also lead to increased hypersensitivity reactions and severity of reactions. The improvement in patient flow and decreased hypersensitivity reactions would translate into associated cost benefits.

To the best of our knowledge, no data exists regarding priming intravenous administrations sets with monoclonal antibodies to reduce chair time. Laudati, Clark, Knezevic, Zhang and Barton-Burke, 2018, investigated priming practice to reduce hypersensitivity reaction, but did not collect chair time.

METHODS

Research aims

The research aims to determine whether priming intravenous administration sets with monoclonal antibodies will reduce chair time in the outpatient setting.

Primary Outcome

Chair time as measured by duration of infusion. (From the time the infusion commenced until the time the infusion completed).Secondary Outcome

The secondary outcome of this study is to evaluate whether priming intravenous administration sets with monoclonal antibodies will reduce hypersensitivity reactions.

The secondary outcome will also include:

1. The time of onset to infusion related hypersensitivity reactions
2. Incidence of medical emergencies as a result of hypersensitivity reactions
3. Admissions to hospital due to hypersensitivity reactions
4. And any delays or reductions in treatment regimens due to hypersensitivity reactions
5. Patient experience (please refer to appendix 2)

Study design

This is a randomised controlled trial with a two-group design comparing primed intravenous administration sets with monoclonal antibodies to non-primed administration sets to assess reduction in chair time.

Hypothesis

We hypothesis that there will be a significant decrease in chair time when an intravenous administration set is primed with the monoclonal antibody

Sampling framework

The sample will include a group of patients receiving the monoclonal antibodies; Daratumumab, Obinutuzumab, Pembrolizumab and Nivolumab for Haematological and Oncological malignancies at the RBWH Oncology Day Therapy Unit and Oncology Procedure Unit.

Setting

The sample will include a group of patients receiving monoclonal antibodies in The Oncology Day Therapy Unit or Oncology Procedure Unit at the RBWH.

Sample Size and Justification

In consideration of the aim and scope of the study, a sample size of 128 episodes of care, 32 episodes per monoclonal antibody was determined to be feasible. For an independent group design a sample size of 51 is required to detect a medium effect size of 0.5 (Cohen's d) with 80% power and alpha of 0.05. To account for the episodes of care the sample size was inflated using a design effect of 1.2, therefore requiring approximately 64 per group.

To the best of our knowledge, no data exists regarding priming intravenous administrations sets with monoclonal antibodies to reduce chair time. This has presented challenges with performing sample size calculations

Selection Criteria

All patients presenting to the Oncology Day Therapy Unit and the Oncology Procedure Unit for the single agent Intravenous Monoclonal Antibodies; Nivolumab, Pembrolizumab, Daratumumab and Obinutuzumab. The inclusion and exclusion criteria will be considered for participation in this RCT.

Inclusion Criteria

1. Patients attending the Oncology Day Therapy Unit or Oncology Procedure Unit
2. 18 years or older
3. Are being treated with the single agent monoclonal antibodies: Obinutuzumab, Daratumumab, Nivolumab, Pembrolizumab.
4. Any cycle of a patient's treatment regime (e.g, 1st, 2nd, 3rd dose)

Exclusion Criteria

1. Under 18 years of age
2. Patients receiving treatment with a monoclonal antibody as an inpatient or at North Lakes
3. Patients receiving any other monoclonal antibodies that do not meet the criteria of inclusion drugs, chemotherapy, supportive therapies or treatment as part of a pharmaceutical clinical trial
4. No funding to approach patients who require a translator

Screening, recruitment and consent

A research nurse will refer to the scheduling in the Oncology Day Therapy Unit and Oncology Procedure Unit to identify the patients who will receive monoclonal antibodies. The research nurse will then screen and gain consent from the patients receiving a monoclonal antibody in the outpatient setting. The research nurse will ensure the screened patients meet the inclusion criteria. Eligible patients will be given information on the study. These patients will be given the opportunity to ask any questions about the study. Once the patients are satisfied with the information and agree to participate in the study, the research nurse will ask them to sign consent.

Randomisation, allocation and blinding

Randomisation will conform with best practice standards for randomisation generation and allocation concealment until study entry. This will be done through REDCap. We will stratify by monoclonal antibody to ensure that 16 people per drug will end up in each group. Randomisation will be on a 1:1 ratio between groups with randomly varied block sizes. Data will be collected through a completed Data Collection Tool and patient notes. Due to the nature of the study, it is not possible to blind participants and research investigators.

DATA COLLECTION

Baseline data

Patient demographics

- Age
- Disease/ Diagnosis
- Treatment Protocol
- Previous drug reactions

Treatment

- Monoclonal Antibody
- Start time of monoclonal antibody (from the time the infusion commenced)
- Stop time of monoclonal antibody (time the infusion completed, including the flush of compatible fluid)

Venous access device

- Data will be collected from the patient's progress notes and the data collection form (Appendix 1.) to obtain whether the patient had a CVAD or PIVC.

Data for Primary outcome

Chair time

- Time infusion started (from the time the infusion commenced)
- To time infusion stopped (time the infusion completed, including the flush of compatible fluid)
- See Data collection form (Appendix 1.)

Data for Secondary outcomes

The time of onset to hypersensitivity reactions

- The data collection form is to be completed by the registered nurse or clinical nurse attending to the patient receiving treatment. This form will require start and stop times of the monoclonal antibody, as well as stop or recommencement times for the monoclonal antibody if a reaction occurs. (Appendix 1.)
- Data will be collected from the patient's progress notes and medication chart to assess the type of reaction that occurred and if the reaction was a MERT.
- Management of reactions will be as per EVIQ, Manual of Procedures or the treatment protocol.
- Data will be verified against risk man.
- Data will be collected from the patient's progress notes and medication charts to assess for any delays in treatments or admissions to the ward.
- Patient experience surveys will be collected.

DATA ANALYSIS

All data will be entered directly into the software REDCap (Metro North Hospital and Health Services) and exported for analysis. Prior to analysis, data cleaning of outlying figures, missing and implausible data will be undertaken. Success of randomisation will be determined by comparing the control and intervention groups.

Primary outcome

Mean chair time will be compared between groups using General Estimating Equations to account for episodes of care within the same person, with adjustment for drug type. Means and 95% confidence intervals will be reported. Residuals of models will be checked for the assumptions using descriptive statistics and plots. If assumptions are violated the data will be log transformed or bootstrapped as appropriate.

Secondary outcomes

Secondary outcomes such as adverse events will be described with descriptive statistics and tested using basic statistical test such as fishers exact due to the expected low number of events.

ETHICAL CONSIDERATIONS

This research will be reviewed by the RBWH Human Research and Ethics Committee (HREC). The trial will be registered with the Australian and New Zealand Clinical Trial Registry (ANZCTR). Hypersensitivity events will be recorded in riskman.

MANAGEMENT OF DATA

Hospital Data

All data collected in relation to this study will be kept in a secure locked cabinet located within the premises of the Centre of Clinical Nursing, RBWH Campus, Herston.

The management and storage of data in this project will conform to the requirements of the National Health and Medical Research Council (NHMRC) and National Statement on Ethical Conduct in Human Research (2007) guidelines. No identifying participant information will be recorded on the online platforms. Participant confidentiality will be assured. All electronic data will be de-identified and collected on a password protected database. A screening log will be kept independently from the electronic database and stored in a locked filing cabinet in a locked room. Fifteen years after

results are finalised, electronic files and paper documents will be destroyed (NHMRC, 2015). Data used in publications will be de-identified and reported as group data to ensure confidentiality.

STUDY DATA

All data generated in this study will remain confidential. All participants will be assigned a unique study identification number; therefore, no identifying participant data will be available for use.

SAFETY REPORTING

Definitions

1. An Adverse Event (AE) is any untoward medical occurrence in a patient, which may or may not necessarily have a causal relationship with this intervention.
2. A Serious Adverse Event (SAE) is any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity.

Adverse Events

Adverse events occurring concurrently or as a result of receiving a monoclonal antibody would be addressed in accordance with RBWH policies, procedures and guidelines. Serious adverse events, such as death and unplanned admissions to hospital or the intensive care unit, will be reported to the RBWH HREC.

Safety Reporting

Safety monitoring will be conducted after the first 30 patients.

POTENTIAL RISKS AND BENEFITS

Risks

There are minor risks associated with participation in this study regarding both the intervention and data collection aspects of this study. The potential risks of participation will be explained to participants in the Participant Information Sheet section of the Patient Informed Consent Form.

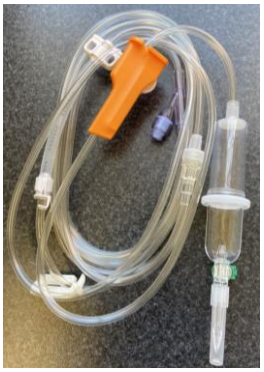
Priming practice

There are multiple different administration sets. This is something that will be discussed to ensure the safest way to achieve the outcome of the length that needs to be primed to avoid any risks involved with patients receiving the monoclonal antibody at the prime rate.

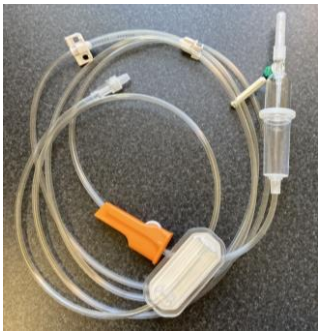
- **The prime volume will be 16mls**
- **The flush volume of compatible fluid will remain at 50mls**

Intravenous administration sets to be used:

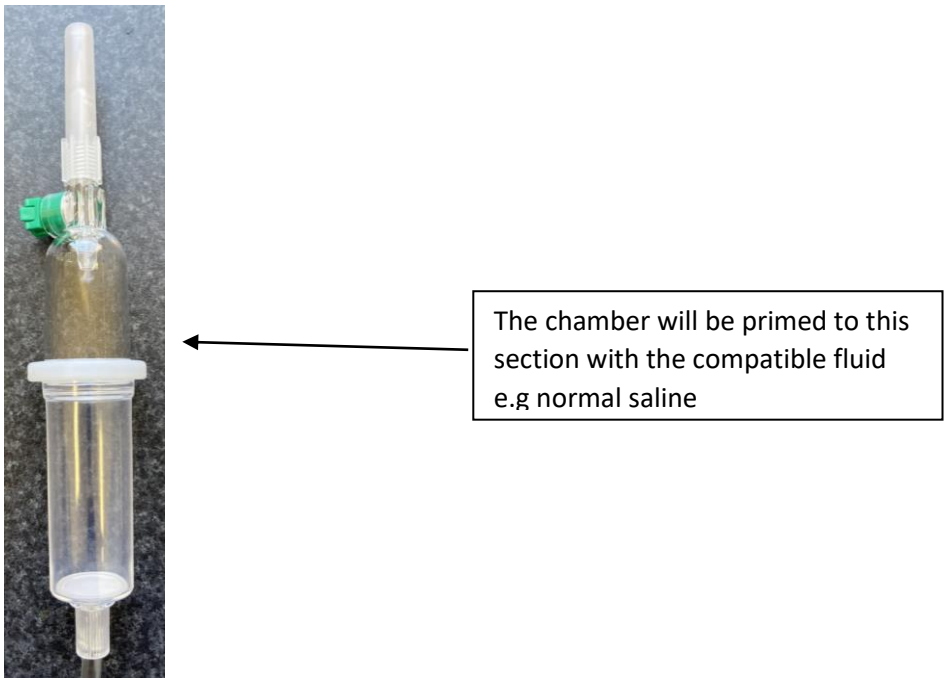
- **Infusomat Space line for Obinutuzumab**



- **0.2 Micron in-line filter for Nivolumab, Pembrolizumab and Daratumumab**



- **IV line to be primed with a compatible solution e.g. normal saline.**



Administration rates

Obinutuzumab and daratumumab are administered in accordance with the product information at an incremental rate that increases during the infusion if there is no reaction, up to a maximal infusion rate. Pembrolizumab and nivolumab are administered at a flat rate over the specified infusion duration (no increments).

LIMITATIONS OF RESEARCH

The limitations of research that may be encountered are cofounders including the length of the primed line. This is due to the multiple different administration sets. This is something that will be discussed to ensure the safest way to achieve the outcome of the length that needs to be primed.

Further cofounders will be whether the patient has a central venous access device or a peripheral intravenous catheter due to the lengths of the different devices.

VALIDITY

Internal

This RCT is a single centre study conducted in Cancer Care Services, RBWH, Herston, ensuring consistency and continuity in recruitment and data collection and analysis. Pre-procedure consent will be gained prior to each treatment. This will ascertain the existence of any patient concerns.

The nursing data collection form will apply to both the control group and the intervention group. Patients assigned to the control group will not have their treatment primed with the monoclonal antibody and those patients in the experimental group will commence their monoclonal antibody with a monoclonal antibody primed line.

External

RBWH is a quaternary public hospital whose patient population is representational of many ethnicities. However, with the small sample size (128) the group treated may not be generalisable to another population.

TIME FRAME & FEASIBILITY OF RECRUITMENT

Non-statistical considerations were considered such as time and resources. It will take approximately 3 months to recruit our sample size of 128 patients, 32 patients per group.

PEMBROLIZUMAB	9	3	1	8	13	34
NIVOLUMAB	5	5	5	16	8	39
OBINUTUZUMAB	2	3	4	1	3	13
DARATUMUMAB	2	2	4	3	5	16

The table below shows daily treatment totals for each monoclonal antibody for a period of 5 weeks. This was calculated from the 25th of February to the 27th of March for ODTU and OPU:

FUNDING

This RCT is currently unfunded. This RCT is supported by ODTU and the nursing team. An ODTU nurse is off-line to complete the 12-month Evidence-Based Research Internship occurring one (1) day per week with support from the Nursing Research Department and funded through RBWH Cancer Care Services.

DISSEMINATION OF RESULTS

The results of this research will be disseminated within the RBWH, and at relevant local, national and international oncology scientific meetings. The pilot study will be published in a relevant healthcare journal and written in accordance with the CONSORT statement recommendations.

APPENDIX 1.

NURSING DATA COLLECTION FORM

Please provide the name of the monoclonal antibody here:

Please tick the box to indicate whether the patient has a CVAD or PIVC

	CVAD

PICC	
PORT-A-CATH	
HICKMAN	

PIVC

Please complete the following table.

If no disruptions to treatment, please just fill out the start and stop time of the monoclonal antibody:

Start Time:	
Stop Time:	
Stop time if disruption:	
Re commencement time:	
Reason for Stopping if disruption:	

APPENDIX 2.

PATIENT SURVEY

DATE:

STUDY NO:

This study aims to reduce the time spent in the outpatient setting. Your participation in the 'Priming Practice' Study is greatly appreciated. To understand your experience, we would like to ask you a few questions. Thank you, we really appreciate your time.	
Did you receive adequate information about how to recognise an infusion reaction?	

Were you satisfied with the duration of your treatment today?	
What could we do to improve the service?	
If there is anything else you would like to say, please add it in this space:	

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