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Reducing harm from paclitaxel infusion using titration rate: A quality improvement project

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ABSTRACT

Background: The number of paclitaxel infusion reactions was observed as the highest among all Cancer Medication Infusion Reactions (CMIR) in the Cancer Care and Hematology Clinic at Scarborough Health Network (SHN) despite the use of pre-medication. This quality improvement project was aimed at reducing the number of paclitaxel reactions and reducing extended chair time due to infusion reactions.

Method: Our quality improvement strategy focused on monitoring paclitaxel reaction rates while using a standardized titration rate strategy for patients receiving the first three lifetime cycles of paclitaxel infusion for solid tumours or hematologic malignancies. The titration rate was calculated with a variety of drug volumes that are used within the Scarborough Health Network. Findings from the 4 months of piloting the titration rate strategy were compared to the previous 4 months when titration rates were not used.

Result: Four months after introducing the new strategy, there were 35.71% paclitaxel reactions when a titration rate was used as compared to 51.35% reactions when a titration rate was not used. Patients who received paclitaxel infusion using titration rates increased the scheduled chair time to 30 minutes to allow for slower infusion rates, while patients with hypersensitivity reactions (HSRs) required an extra 3 hours of chair time that was not pre-planned.

Conclusion: There were fewer HSRs after the launch of the titration rate strategy in patients receiving paclitaxel for the first three lifetime cycles. This strategy also reduced overall chair time at the clinic.

Keywords: cancer, chemotherapy, hypersensitive reactions (HSRs), Paclitaxel, infusion reaction, titration rate

BACKGROUND

Paclitaxel is a chemotherapy medication that is indicated, alone or in combination, for the treatment of various types of cancer including breast, lung, and ovarian cancer (Bocci et al., 2013). It is administered intravenously over 1 hour or 3 hours depending on the patient's protocol. The infusion rate can vary based on the medication dose, and the specific cancer being treated. Patients receiving paclitaxel are at risk for developing hypersensitivity reactions (HSRs) primarily during first and second lifetime exposures (Lynch et al., 2023). Symons et al. (2024) reported that 30% to 40% of the patients experience HSRs without pre-medications. This number decreases to 5% to 10% when pre-medications are given.

HSRs related to paclitaxel usually occur during the first 10 minutes to an hour of the infusion, especially during the first or second lifetime exposures (cited by Myers, 2000). The common symptoms occur within minutes and include hypotension, flushing, dyspnea, throat tightness, and chest or back pain (Tsao et al., 2021). The grade of HSRs is from mild transient symptoms to life-threatening (see Table 1). Premedication is commonly used to decrease HSRs and can include dexamethasone, diphenhydramine, and an H2-histamine antagonist, such as cimetidine, ranitidine, or famotidine (Ontario Health–Cancer Care Ontario [OH-CCO], 2024). However, although premedication has successfully decreased HSRs, there are still many HSRs being observed at our facility.

Data from the hospital administrative database showed high rates of infusion reactions. Data from May 2022 to

May 2023 for the Scarborough Health Network (SHN) Cancer Care Clinic at Centenary Hospital indicated that 50% of the infusion reactions were from paclitaxel (Table 2). In the same period, the SHN Cancer Care Clinic at the General Hospital had 42% of reactions from paclitaxel. Data from April 2022 to July 2023, combined for both General and Centenary hospitals of SHN, indicated that 50 out of 124 reactions were from paclitaxel or 40.3% of all cancer medication infusion reactions (CMIRs). More recent data were examined through the CMIR report built from the electronic clinical information system (CIS). Data from July 1 to Nov 2, 2023, from both General and Centenary hospitals of SHN, indicated that 19 out of 37 infusion reactions were from paclitaxel or 51.3% of all CMIRs. Managing the frequent infusion reactions from the commonly used chemotherapy paclitaxel have not only increased stress for nurses in an already highly demanding working environment, but also increased distress to patients and families.

Paclitaxel was being infused in our setting using administration guidelines from Ontario Health Cancer Care Ontario (OH-CCO) and the product monograph. However, there was no titration rate and little supportive research available to guide practice. Wanting to keep patients' safety and comfort in mind during the highest stressful time for patients, when patients are newly diagnosed and getting their first treatment, we decided the preferred approach would be the strategy of titrating the medication. Two independent studies by Lynch et al. (2023) and Kofi Sefah et al. (2023) were the basis for this quality improvement initiative at SHN. Lynch et al. (2023) and Kofi Sefah et al. (2023) reported significant reductions in the rate of infusion-related hypersensitivity reactions in patients receiving their

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Table 1

Grade of Reactions

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

Note. Reference: *Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0* Published: November 27, 2017. NSAIDs = non-steroidal anti-inflammatory drugs.

Table 2

List of Chemotherapy Drugs Infused Between May 2022 to May 2023 and Their Reaction Incidence Rates – SHN Centenary and General Hospital

Drug Generic Name Ordered	Centenary Hospital Incidents	Centenary % of Total Incidents	General Hospital Incidents	General % of Total Incidents
avelumab	2	5%	2	2%
Benadryl	0	0%	1	1%
bendamustine	1	3%	1	1%
CARBOplatin	1	3%	2	2%
CISplatin	0	0%	1	1%
daratumumab	0	0%	1	1%
DOCEtaxel	0	0%	4	5%
Hydrocortisone	0	0%	1	1%
irinotecan	2	5%	3	3%
leucovorin	1	3%	0	0%
nivolumab	1	3%	3	3%
oBINutuzumab	1	3%	1	1%
oxaliplatin	3	7%	13	16%
PACLitaxel	19	50%	37	42%
riTUXimab	6	15%	14	16%
trastuzumab	1	3%	2	2%
Total	38	100%	89	100%

first and second lifetime doses of paclitaxel by using the titration rate. Thus, the overall aim of our quality improvement project was to reduce the number of reactions by implementing a titration rate strategy for the patients who were receiving their first three lifetime exposures to paclitaxel. Although the reactions are mostly at the first two doses, as mentioned in the drug

monograph (Sandoz, 2021) and Lynch et al. (2023) and Kofi Sefah et al. (2023), there are instances where reactions are observed at the third dose. Therefore, to pilot the implementation, the first three doses were titrated.

The other important issue related to infusion reactions in a busy oncology clinic is chair time. The frequent infusion reactions increase the chair

time by approximately 3 hours or more, depending on the grade of reaction. The increased chair time due to reactions interrupts the scheduled appointments, impacting both staff and patients. Thus, our intention in reducing HSRs related to paclitaxel was also to benefit the following:

- to reduce treatment interruptions, delays, and discontinuations

- to decrease the number and severity of immediate HSRs during the first three lifetime exposures to paclitaxel
- to reduce patient harm due to HSRs, by increasing the tolerability of the drug
- to decrease patient and family distress due to HSRs
- to reduce the use of HSR medications
- and to save chair time.

METHODOLOGY AND IMPLEMENTATION

The quality improvement project used a four-step approach: 1) a literature search was conducted focused on titration rates for paclitaxel infusions; 2) a standardized titration rate was created; 3) the staff education and implementation of the titration rate for the first three cycles of paclitaxel infusion was introduced; and 4) the evaluation of the effectiveness of the titration rate was conducted by auditing the infusion reactions data in the clinic.

Step 1: Internet Explorer and SHN library resources were used as search engines for published articles. The keywords used to generate the search were ‘infusion reaction’, ‘Paclitaxel’, and ‘Hypersensitivity reaction to Paclitaxel’.

The supported studies along with past statistics on paclitaxel infusion reaction from the SHN database were shared at the monthly medical oncology meeting. The proposal for a pilot project of titration rate was developed by the clinical practice leader and agreed upon by the SHN medical oncology group members and the oncology leadership.

Step 2: The titration rate strategy was created by the clinical practice leader based on the “*Hypersensitivity and Acute Infusion Reactions to Chemotherapy/Biotherapy Treatment Algorithm*” (OH-CCO, 2019). This guide is used in the event of hypersensitivity reaction to any chemotherapy drug. A paclitaxel titration rate poster was developed, considering the dose and volume of paclitaxel infusion bags, and reviewed by the oncology pharmacy at SHN for rate calculation verification. Both studies by Lynch et al. (2023) and Kofi Sefah et al. (2023) reported higher incidence rates of infusion reactions in the first two

Figure 1

Change in PACLitaxel Infusion Reactions with and Without Titration

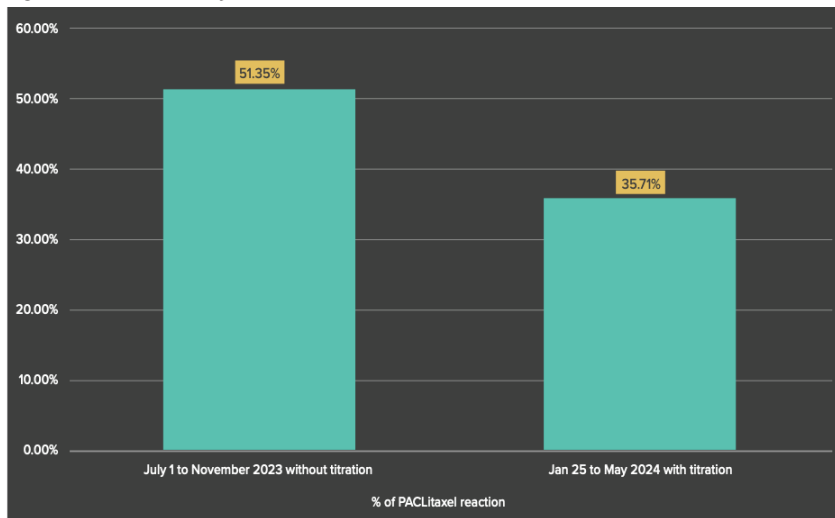


Figure 2

Percentage of PACLitaxel Infusion Reaction According to the Dose Number

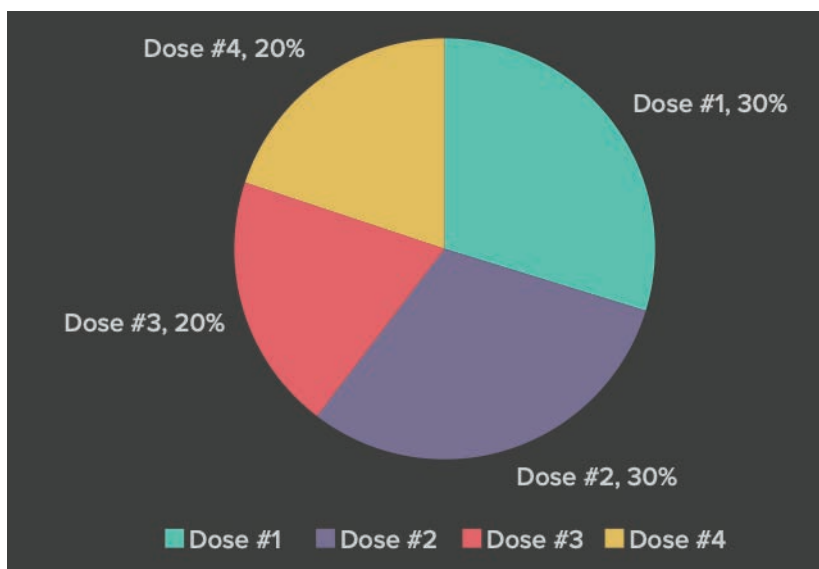
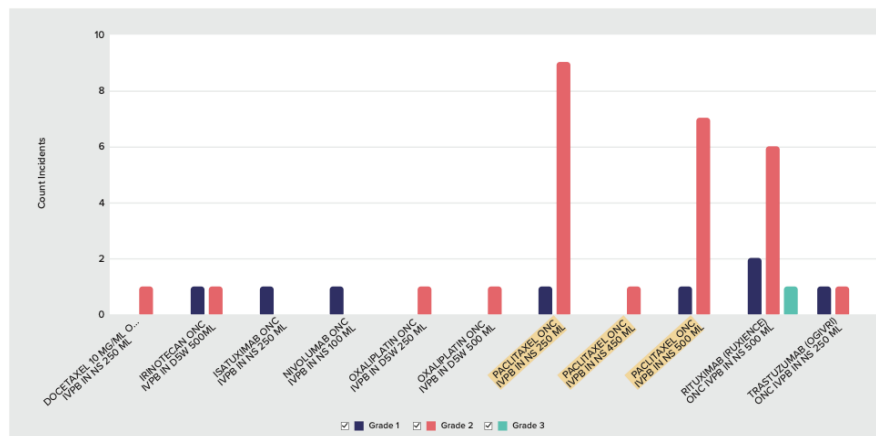


Figure 3

Reaction Incidence of PACLitaxel Infusion Without Titration July 1 to November 30, 2023



lifetime cycles. However, based on the data at the SHN, it was decided to keep the titration rate for the first three cycles to assess the reduction of the reaction rate.

The rate increments from the OH-CCO algorithm were used for paclitaxel infusions for the first three life-time doses. These increments are 25% of the calculated final rate, then 50% of the calculated final rate, and 75% of the calculated final rate to 100% of the final rate. The titration rate was calculated with a variety of drug volumes that are used at the SHN, such as 250ml in one hour, 500ml in three hours, 100ml in one hour, 250ml in three hours, and 500ml in one hour. Each titration increment has a 10-minute interval. At each titration, the nurse assesses the patient using a subjective and objective nursing assessment, including vital signs, voiced concerns, and any signs or symptoms of a reaction.

Step 3: Staff education related to the titration rate for paclitaxel and documentation related to CMIRs were provided to nurses before and during the implementation phase. The titration rate strategy was implemented by the nurses.

Step 4: Close monitoring of CMIR data

was conducted by the clinical practice leader with attention to reactions related to paclitaxel. These incidence data were then shared with the oncology team on a monthly basis.

Outcomes: In our quality improvement study, we collected data on HSRs (incidence, severity) and duration of extended chair time with titration rate and chair time due to HSRs.

Analysis: Data for a 4-month period of time before initiating the titration rate strategy was compared to a 4-month period of time after initiating the titration rate strategy using the intention to treat descriptive analysis. This means that we report on all HSRs before and after initiation of the titration strategy whether or not the nurses applied the titration rate strategy. Chair time was measured in minutes.

RESULTS

Literature Search

There were 29 articles generated from the literature search. Only two short articles were related to successful titration rate and HSRs to paclitaxel. Both studies by Lynch et al. (2023) and Kofi Sefah et al. (2023) reported

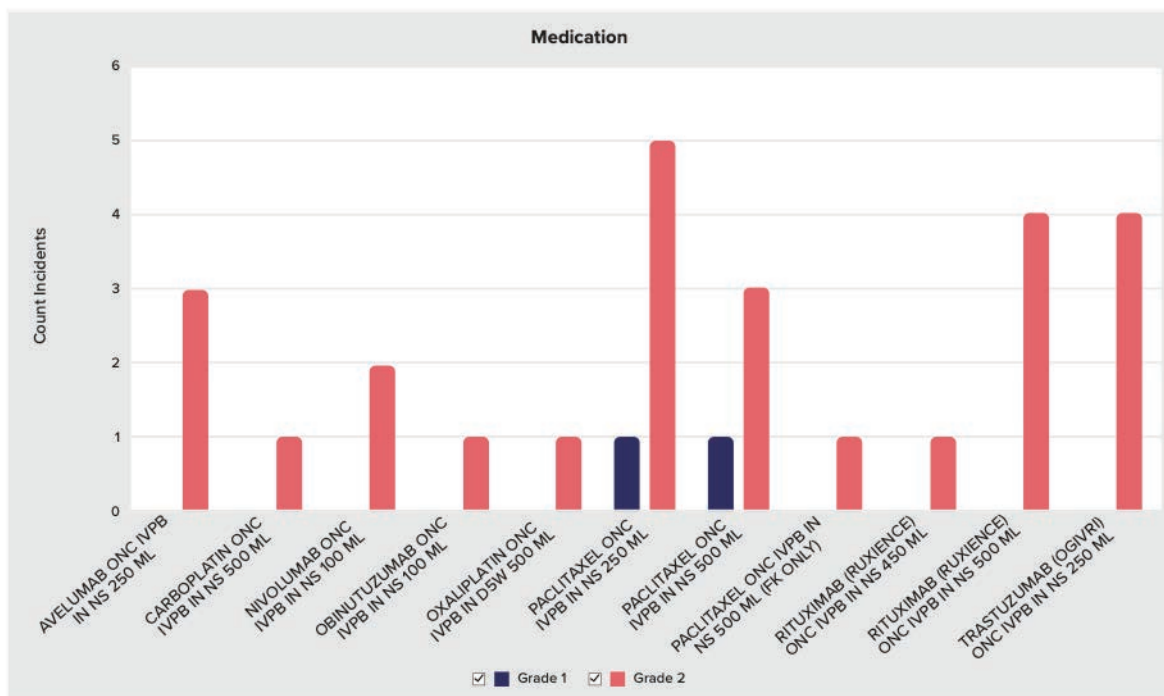
a significant reduction in the rate of infusion-related hypersensitivity reactions in patients receiving their first and second doses of paclitaxel by using the titration rate strategy. Lynch et al. (2023) indicated the non-titrated group had 19% of the reactions whereas the titrated group had only 7%. Kofi Sefah et al. (2023) reported hypersensitivity reactions occurred in 4.8% of the titration group and 18.3% in the standard-of-care group or non-titrated group.

Infusion reaction results

The comparative analysis was conducted 4 months after the launch of the titration rate used for paclitaxel infusions. For the pre-titration data, from July 1 to Nov. 2, 2023, infusion reactions from both General Hospital and Centenary Hospital Cancer Clinic of SHN indicated that 19 out of 37 infusion reactions were from paclitaxel, which is 51.3% of all CMIRs. The infusion reaction data after the launch of titration, from Jan. 25 to May 30, 2024 (Figure 4) revealed that 10 out of 28 CMIRs were from paclitaxel, which is 35.71% of all CMIRs. A total reduction of 16.25% in the paclitaxel reactions was observed using the titration rate.

Out of 35.71% of the reactions where

Figure 4



titration rate was used, 60% of the reactions were from dose 1 and dose 2, 20% of the reactions were from dose three, and 20% were from dose four. Ten percent of reactions at dose three were those where titration rate was missed at the initiation of the paclitaxel infusion. This has confirmed that titration rate at dose three is a successful strategy to reduce the reactions.

Out of the 35.71%, 90% of reactions were grade 2 and 10% were grade 1. There were no grade 3 reactions reported. The average paclitaxel reactions were detected at 21.7 minutes of infusion with approximately 28–30ml of infusion absorbed. The early detection of the reaction gave a chance for nurses to implement the HSR interventions. With early intervention of reactions patients are more likely to complete their treatment without delays and interruptions.

Chair time results

Chair time was another consideration with this QI project. With paclitaxel reaction without titration, the chair time increased up to three hours or more, depending on the severity of the reactions. With the introduction of the titration rate, the chair time increased to 30 minutes. Considering that only an increased 30 minutes was needed for the titration strategy for paclitaxel patients, it has saved on the unexpected chair time. Overall, a shorter time is required to deal with reactions and has minimized the interruption in the clinic’s scheduled appointments. With frequent infusion reactions, there is a cascading effect on the next patient’s appointment in line.

DISCUSSION

Our quality improvement project showed that implementing the titration rate strategy for the first three lifetime doses of paclitaxel reduced the number of HSRs and the length of additional chair time needed for managing HSRs. As well, the severity of HSRs for those receiving the titrated rates was described as mild to moderate without life-threatening reactions. Although each patient receiving paclitaxel required an extra 30 minutes of chair time, there were fewer

Table 4

Reaction Incidence of PACLitaxel Infusion Without Titration From April 2022 to July 2023 (prior to introducing the new strategy)

Drug Generic Name Ordered	# of Incidents	% Total of Incidents
avelumab IV	3	2%
Benadryl	1	1%
bendamustine	1	1%
bleomycin	1	1%
CARBOplatin	2	2%
CISplatin	1	1%
daratumumab	1	1%
DOCEtaxel	5	4%
etoposide	1	1%
Firmagon	1	1%
Hydrocortisone	1	1%
irinotecan	3	2%
isatuximab	1	1%
Kadcyla trastuzumab emtansine	1	1%
leucovorin	1	1%
MonoFerric	1	1%
nivolumab	4	3%
oBINutuzumab	1	1%
oxaliplatin IV	16	12%
<u>PACLitaxel</u>	50	40%
PERTuzumab	1	1%
riTUXimab	23	18%
trastuzumab	4	3%
Total	124	100%

HSRs. Overall, the strategy saved the unexpected lengthy chair time required to manage the unexpected HSRs. Hence, our titration strategy has minimized the interruption in the clinic’s scheduled appointments.

Implementing the titration rate for paclitaxel infusion for the first three lifetime doses showed a significant decrease in paclitaxel infusion reactions. The 16% reduction in HSRs observed in our quality improvement project was slightly larger than the 12% to 14% reported in

the literature (Lynch 2023; Kohn 2023). This difference could have been because we continued the titration rate strategy for the third lifetime dose of paclitaxel, whereas the studies focused only on the first two lifetime doses. This has also reduced the overall CMIR rate at the SHN oncology clinic.

We believe the resulting benefit of titration rates included patients’ increased tolerability of the drug, reduced use of HSR medications during the infusion, and a higher likelihood

of completing the paclitaxel treatment without interruption. Nurses following our standardized titrate rate strategy were able to catch the reactions early and intervene appropriately. Additional measurement of these variables in a future project would be helpful.

There are a few limitations to consider. First, this was a single-site project and we only monitored data for four months before and after the initiation of the titration rate strategy. It would be of benefit to monitor HSRs for a longer period of time and formally measure chair time to demonstrate the actual reduction.

CONCLUSION

The quality improvement project demonstrated a 16.25% reduction in paclitaxel infusion HSRs using our new titration rate strategy. Although the titration rate strategy required a scheduled increased chair time of an extra 30 minutes, an unplanned HSR reaction chair time typically increases up to 3 or more hours. With the implementation of the titration rate strategy, there were fewer reactions and fewer interruptions in the clinic's scheduled appointments. Informally, nurses expressed their higher comfort in starting the initial paclitaxel doses, and patients and their family members felt less distressed with fewer HSRs occurring in the clinic.

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Table 5

Overview of PACLitaxel Infusion Data from July 2023 to May 2024

July 1 to November 2023 without titration	
Prior to the new infusion titration rate strategy	51.35% PACLitaxel reactions
January 25 to May 2024 with titration	
After introducing infusion titration rate strategy	35.71% PACLitaxel reactions
90% reactions with titration	Grade 2
10% reactions with titration	Grade 1
Approx. volume infused upon reaction	28–30 MLs
Average reaction time	21.7 mins
Reaction at Dose 1	30%
Reaction at Dose 2	30%
Reaction at Dose 3	20%
Reaction at Dose 4	20%
Plan interrupted/discontinued	10% at Dose 3, here titration was missed
Total reduction in PACLitaxel reactions with the use of titration rate	16.25%