Received: 4 July 2022 | Revised: 12 January 2023 | Accepted: 23 March 2023

DOI: 10.1111/ajr.12984

ORIGINAL RESEARCH

AJRH National Rural Health Alliance WILEY

Administration of immune checkpoint inhibitors at rural towns using the Teleoncology model of care—A North Queensland perspective

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Abstract

Objective: This study aimed at evaluating the safety of administering immune checkpoint inhibitors (ICIs) and monitoring for immune-related adverse events (irAEs) using the Teleoncology model of care.

Design: A retrospective cohort study comparing two patient groups.

Setting: The North Queensland Teleoncology Network (NQTN) operated by the Townsville (THHS) and Cairns Hospital Health Services (CHHS) with the Townsville Cancer Centre (TCC) acting as the control group setting.

Participants: Patients who received ICI treatment via the NQTN between January 2015 and April 2019. Patients who received ICI at the TCC over the same time period were used for comparison.

Main Outcome Measures: Rates of high-grade irAEs and irAE-related deaths.

Results: Fifty-two patients received a total of 822 cycles of ICIs via the Teleoncology model through NQTN. Over the same time period, 142 patients received a total of 1521 cycles at the TCC. There were no significant differences in all demographic characteristics between either group, including tumour profile and Indigenous status. There were no statistically significant differences between the rates of high-grade irAE across multiple body organ systems ($p = 0.151$) and rate of hospital admissions (13.5% (NQTN) vs 5.6% (TCC), $p = 0.702$). There were no irAE-related deaths in either group.

Conclusions: The results suggest that with adequate governance and clinical resources, ICIs can be administered safely using Teleoncology models to rural and remote towns.

KEYWORDS

immunotherapy, irAE, QReCS, safety, telehealth

1 | INTRODUCTION

Despite advances in cancer care, outcomes for patients with cancer living in rural and remote areas of Australia are generally worse when compared to those in metropolitan areas. The latest Australian data demonstrated decreasing 5-year survival rates with increasing geographical remoteness.[1] There are a number of factors that contribute to this including limited access to oncology specialists and other health professionals including chemotherapy-competent nurses in these geographical areas of need.[2,3]

One of the established ways of bridging this gap is through the adoption of the Teleoncology model of care by healthcare facilities.[3] The model utilises telehealth systems to provide oncology specialist review with the support of a rural generalist health professional for patients in rural and remote regions. Additionally, systemic treatments are administered locally under the supervision of chemotherapy competent nurses via telenursing platforms. This minimises the need for long-distance travel to a larger cancer centre for patients living in these areas who would otherwise travel despite a high disability burden and face out-of-pocket expenses. Previous studies on the model have demonstrated high rates of patient and health professional satisfaction, timely access to care locally, safety of remote supervision and reduction in costs related to travel and relocation.[4–6]

In North Queensland, this service is provided through the healthcare facilities of the Townsville Hospital (THHS) and the Cairns and Hinterland Hospital Health Services (CHHS) under the governance of the Queensland Remote Chemotherapy Supervision model (QReCS).[7] The model enables provision of expert cancer care and systemic treatment administration to satellite centres at the Townsville, Mackay, Mount Isa, Atherton, Innisfail, Thursday Island and Weipa health districts. Distances between the facilities and their network satellite sites range from 100 to 1200 kilometres.[8]

In 2010, a landmark trial by Hodi et al demonstrated significant survival outcomes in the treatment of metastatic melanoma with ipilimumab, an immune checkpoint inhibitor (ICI).[9] Since then, the role of ICIs, primarily anti-cytotoxic T lymphocyte antigen 4 (CTLA4) and anti-Programmed Cell Death 1 (PD1) monoclonal antibodies, in the treatment of various cancers has expanded rapidly with improvement in clinical outcomes for the patient with cancer.[10]

Despite their therapeutic efficacy, ICI treatments are associated with a unique side effect profile termed immune-related adverse events (irAEs) that are believed to arise from an augmented immune system.[10] We have demonstrated in a previous study that conventional chemotherapy can be administered using the Teleoncology model with safety outcomes comparable with a tertiary centre.[11] However, the safety of monitoring for irAEs through this model has not been examined since its implementation. This study evaluates the safety of administering ICIs through the Teleoncology model of care by comparing patient morbidity and mortality outcomes with those who received ICIs directly at a tertiary centre, Townsville Cancer Centre (TCC).

What is already known on this subject?

- Teleoncology models allow safe administration of conventional chemotherapy to rural towns.
- The safety of administering immune checkpoint inhibitors using the model, however, has not been previously examined.

What this paper adds

- This study suggests administering immune checkpoint inhibitors to rural towns via Teleoncology models is safe with outcomes comparable with that of a traditional face-to-face approach at a tertiary centre.

2 | MATERIALS AND METHODS

2.1 | Data collection

This retrospective study was conducted at THHS and CHHS healthcare facilities. Clinical information needed for all patients, including those under the Teleoncology group, was acquired through electronic chart reviews of the clinical record system used by oncologists (MOSAIQ Oncology Information system, Elekta, Missouri, USA). The data collected included:

- patient demographics including age, gender, Indigenous status and type of solid organ cancer;
- treatment location within the North Queensland Teleoncology Network (NQTN, comprising of THHS and CHHS Teleoncology networks) or directly at the Townsville Cancer Centre (TCC);
- type of ICI administered, number of treatment cycles and number of treatment delays; and
- ICI toxicity-related information including incidences of high-grade irAEs (Grades 3–4, according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 5.0), hospital admissions related to irAE and mortality outcomes.

2.2 | Patient selection

All patients who had received ICIs via NQTN from January 2015 to April 2019 were included in this study. Similarly, patients who had received ICIs at the TCC within the same period were included for comparison. Patients on trials and those who were receiving dual-agent ICIs as maintenance treatment were excluded from this study as these patients would not have received ICIs via NQTN for safety reasons. All patients were presumed to be clinically fit for ICI treatment.

2.3 | Statistical analysis

All data were collated in a spreadsheet (Microsoft Excel, Microsoft Corp., Washington, USA) and transferred to the Rstudio software Version 1.1.383.11.[12] Data were checked for normality assumptions. Categorical variables were analysed with Fisher's exact tests and numerical values with Mann–Whitney–Wilcoxon tests, with analysis for statistical differences in rates of irAEs and irAE-related hospital admissions between the Teleoncology and face-to-face patient cohorts. Statistical significance was defined as $p < 0.05$.

2.4 | Ethics approval

Ethics approval was obtained from the human research ethics committees of THHS (LNR/2019/QTHS/48698) and CHHS (LNR/2020/QCH/58003).

3 | RESULTS

A total of 52 patients received 822 cycles of ICIs through NQTN. During that same period, 142 patients received a total of 1521 cycles of ICIs directly at the TCC for comparison.

Patient demographics are summarised in Table 1. There were no statistically significant differences in all patient demographic subcategories including the percentage of those who identified as Indigenous. For both groups, advanced pulmonary non-small-cell cancer was the most common cancer (63% for NQTN and 54% for TCC patients) followed by metastatic melanoma, renal cell carcinoma, and head and neck tumours.

Table 2 summarises treatment-related findings for both study groups. Nivolumab was the most common ICI used in both groups (62% for NQTN and 64% for TCC) followed by pembrolizumab and ipilimumab. There was no significant difference in the median number of treatment delays between either group; however, there were a greater proportion of treatment delays within the TCC cohort ($p = 0.013$).

TABLE 1 Demographics of patients treated under the North Queensland Teleoncology Network and at the Townsville Cancer Centre.

Treatment location	North Queensland Teleoncology Network (NQTN) $n = 52$	Townsville Cancer Centre (TCC) $n = 142$	p-Value
Age, years (median, range)	68 (37–86)	64 (31–86)	0.255
Gender			0.112
Male	37 (71%)	101 (71%)	
Female	15 (29%)	41 (29%)	
Ethnicity			0.686
Indigenous	4 (8%)	8 (6%)	
Non-Indigenous	48 (92%)	134 (94%)	
Cancer type			0.455
Advanced non-small-cell lung cancer	33 (63%)	76 (54%)	
Metastatic melanoma	16 (31%)	57 (42%)	
Renal cell carcinoma	3 (6%)	3 (2%)	
Head and neck	0	5 (4%)	
Other	0	1 (1%)	

TABLE 2 Immune checkpoint inhibitor treatment-related findings.

Treatment group	North Queensland Teleoncology Network (NQTN) $n = 52$	Townsville Cancer Centre (TCC) $n = 142$	p-Value
Immunotherapy			0.159
Nivolumab	32 (62%)	91 (64%)	
Pembrolizumab	16 (31%)	51 (36%)	
Ipilimumab	3 (6%)		
Atezolizumab	1 (2%)		
Total number of cycles	822	1521	0.121
Total via telehealth	624 (76%)		
Median number of cycles per patient (range)	9 (1–81)	6 (1–87)	
Total number of treatment delays	42 (5.1%)	173 (11.4%)	0.013
Median number of treatment delays per patient (range)	0 (0–5)	1 (0–26)	0.166
Protocol suspensions (due to irAE-related complications)	8 (15%)	12 (8%)	0.316

TABLE 3 Toxicity profile across patients treated through the North Queensland Teleoncology Network and at the Townsville Cancer Centre treated with checkpoint inhibitors.

Number of Grade 3–4 toxicities (Common Terminology Criteria for Adverse Events (CTCAE), version 5.0)	North Queensland Teleoncology Network (NQTN) $n = 52$	Townsville Cancer Centre (TCC) $n = 142$	p-Value
Gastrointestinal	5 (9.6%)	6 (4.2%)	0.359
Hepatic	0	1 (0.7%)	0.292
Dermatological	1 (1.9%)	0	0.372
Pulmonary	2 (3.8%)	3 (2.1%)	0.501
Cardiac	1 (1.9%)	1 (0.7%)	0.855
Endocrine	0	1 (0.7%)	0.212
Sum of grade 3–4 toxicity incidence	*9 (17.2%)*	*12 (8.5%)*	0.151
Hospital admissions	7 (13.5%)	8 (5.6%)	0.702

Nil statistically significant difference detected at $p < 0.05$.

The Italic values reflect the sum of grade 3–4 toxicity incidence.

3.1 | Safety outcomes

Table 3 summarises the irAE rates across multiple body systems. The most common body system affected by irAEs was gastrointestinal followed by respiratory. There was no statistically significant difference in high-grade (Grades 3 or 4) irAEs between both groups. All documented high-grade irAEs in the NQTN group were admitted into hospital.

There were no statistically significant differences between the rates of high-grade irAE across multiple systems ($p > 0.05$). There was no significant difference in rate of hospital admissions (13.5% (NQTN) vs 5.6% (TCC), $p = 0.702$) between both groups. Two of the patients under the NQTN group with high-grade irAEs were transferred to their nearest tertiary hospital for further clinical management. There were no irAE-related deaths across either group.

4 | DISCUSSION

Despite the clinical benefits from ICI treatment, monitoring for irAEs can be a challenge due to their ability to affect multiple organ systems.[13] Fatal outcomes have been reported from toxicity-related complications in literature.[14] Hence, early detection of toxicity-related symptoms and interruptions to treatment are important to prevent progression to high-grade irAEs.[14] Patients living in rural and remote communities pose additional challenge due

to geographical distances, and Teleoncology models have been set up to provide care closer to home including monitoring of toxicity.[5]

Overall, our study results demonstrate comparable findings across multiple domains between patients managed and monitored through the Teleoncology model and face-to-face care at a tertiary centre. Of note, it is reassuring that the average patient's treatment delay, usually a result of weather-related delays or clinical concern, observed in the Teleoncology model is comparable with that of the tertiary centre. This may reflect the adequacy of governance for safety and quality for these models.[7] Medical oncologists are likely to feel confident in recommending treatment to proceed after telehealth appointments because of the support of health professionals locally at the rural sites and the prompt supply of these biological agents to rural and remote towns ensures timely and effective cancer treatment for patients living in these areas.

Safety outcomes for both study groups were acceptable compared with the existing literature. The rate of high-grade irAEs amongst the NQTN patients (17.2%) was comparable with that of pivotal trials for single-agent ICI therapy (16.3%–26.6%)[15,16] while the rates were particularly low in the control group (8.5%). The higher toxicity reported in the Teleoncology group could be attributed to cautious practice of peripheral hospitals to admit patients with suspected irAEs, contributing to higher recorded toxicity rather than clinical toxicity. It is worth noting, however, that two of the Teleoncology patients who experienced high-grade irAEs were transferred from their peripheral hospital to the nearest tertiary hospital for further management. Ensuring adequate support for peripheral hospitals in the management of high-grade treatment-related toxicities is a vital component of the Teleoncology model.

Limitations to this study include the small sample size of NQTN patients that was limited by the number of patients that had been treated under the Teleoncology model at time of study. The relatively low rates of toxicity in this audit may leave it underpowered to detect a true difference in outcomes, with power calculation at 0.73. The sample size required to detect between-group differences of a clinically significant 15% rate of combined Grade 3–4 irAEs is 165 in the hospital cohort and 83 in the Teleoncology cohort (with 80% power and 0.05 significance level, and ratio of 2:1 (hospital:teleoncology cohort)).

Additionally, as the vast majority of irAEs were gastrointestinal related, we were not able to infer the safety of monitoring irAEs affecting other organ systems through the Teleoncology model. As this was a retrospective study, interpretations of irAE incidences and their grade were heavily dependent on documentation from medical oncologists, physicians in training and oncology nurses and thus may not have accurately represented the true nature of the irAE. Future research may involve larger retrospective audits or prospective safety data. Additionally, the feasibility of administering ICIs through Teleoncology models, including economic evaluation of costs saved to the individual and the health system, could be assessed.

Our study is the first to show that with adequate governance and clinical resources, ICIs can be administered using Teleoncology models to rural and remote towns, with safety outcomes comparable with that of a traditional, face-to-face approach in a tertiary centre. These findings suggest that existing Teleoncology models can be utilised to safely administer new systemic treatments and monitor for their side effects provided their side effect profile can be established with the existing literature. This is important for patients who live in rural and remote areas and would otherwise travel long distances to have access to these treatments due to safety concerns. We believe these findings can be applied to countries with access to immunomodulating agents and where providing access to these treatments may be an issue for patients in geographically isolated towns.

AUTHOR CONTRIBUTIONS

Sebastian Kang: Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; software; validation; visualization; data curation. **James Fletcher:** Conceptualization; investigation; writing – review and editing; data curation. **Saw Htut:** Investigation. **Amy Brown:** Formal analysis; software; methodology; data curation. **Megan Lyle:** Supervision; writing – review and editing. **Sabe Sabesan:** Supervision; writing – review and editing. **Abhishek Joshi:** Supervision; writing – review and editing.

CONFLICTS OF INTEREST STATEMENT

All authors declare no conflicts of interest.

ACKNOWLEDGEMENT

Open access publishing facilitated by James Cook University, as part of the Wiley - James Cook University agreement via the Council of Australian University Librarians.

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How to cite this article: Kang S, Fletcher J, Htut S, Brown A, Lyle M, Sabesan S, et al. Administration of immune checkpoint inhibitors at rural towns using the Teleoncology model of care—A North Queensland perspective. Aust J Rural Health. 2023;31:540–545. https://doi.org/10.1111/ajr.12984