



Contents lists available at ScienceDirect

The Lancet Regional Health - Western Pacific

journal homepage: www.elsevier.com/locate/lanwpc

Research paper

Changes in systemic cancer therapy in Australia during the COVID-19 pandemic: a population-based study

Monica Tang, MBBS^{1,*,#}, Benjamin Daniels, PhD^{1,*}, Maria Aslam, MBBS², Andrea Schaffer, PhD^{1,**}, Sallie-Anne Pearson, PhD^{1,**}¹ Centre for Big Data Research in Health, Faculty of Medicine, UNSW Sydney, Sydney Australia² School of Medicine and Public Health, Faculty of Health, University of Newcastle, Newcastle Australia

ARTICLE INFO

Article history:

Received 5 May 2021

Revised 6 July 2021

Accepted 9 July 2021

Available online 3 August 2021

Keywords:

covid-19

SARS-CoV-2

Antineoplastic Agents

Cancer Chemotherapy Agents

Australia

Interrupted Time Series Analysis

drug utilization

ABSTRACT

Background: Since the emergence of COVID-19 there have been increasing global concerns about delays and/or discontinuations in cancer care. However, it is unclear to what extent systemic cancer therapy was impacted by COVID-19 in countries with relatively low COVID-19 infection rates. We examined changes in systemic cancer therapy in Australia during the COVID-19 pandemic.

Methods: We conducted a national observational study using de-identified records of government-subsidised cancer medicines dispensed to a random 10% sample of Australians between January 2017 to December 2020. We reported monthly dispensing and initiation rates of antineoplastic (chemo-, immuno- and targeted therapy), endocrine and supportive medicines per 100,000 population. We reported monthly discontinuation rates (defined as ≥ 90 days gap between cancer medicine dispensings) per 1,000 people treated. We used interrupted time series analysis to examine changes during times of increased COVID-19 risk and related public health measures (March, April and July 2020).

Findings: Between January 2017 and December 2020, 1,011,255 cancer medicines were dispensed to 51,515 people. Overall, there were no reductions in antineoplastic dispensing or initiation during the COVID-19 pandemic. In March 2020, we observed a temporary increase of 39/100,000 (95% CI: 14 to 65/100,000) in antineoplastic dispensing, driven by immunotherapy and targeted therapy. In April 2020, we observed a temporary decrease in chemotherapy initiation (-2/100,000, 95% CI: -4 to -1/100,000) and temporary increase in discontinuation of all antineoplastic medicines (35/1,000, 95% CI: 20 to 51/1,000), but these changes were not sustained.

Interpretation: The effective control of COVID-19 in Australia appears to have mitigated the initial impact of COVID-19 on systemic cancer therapy. We observed only small and temporary changes in the use of some cancer medicines early in the pandemic.

Funding: National Health and Medical Research Council; National Breast Cancer Foundation; Translational Cancer Research Network, supported by the Cancer Institute NSW.

© 2021 The Author(s). Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Corresponding author. Monica Tang. Centre for Big Data Research in Health, Faculty of Medicine, UNSW Sydney, Level 2, AGSM Building (G27), UNSW SYDNEY NSW 2052 Australia.

E-mail address: monica.tang@unsw.edu.au (M. Tang).

* equal contributions as first authors.

** equal contributions as last authors.

RESEARCH IN CONTEXT

Spread of the COVID-19 pandemic to Australia prompted lockdowns, changes to health services and formulation of consensus guidelines to guide risk management for people with cancer. There has been concern about the impact of these changes on cancer care and outcomes. Although cancer registry data show a reduction in cancer diagnoses in Australia from April to October 2020, it is not known whether systemic cancer therapy altered significantly in the context of the pandemic.

We identified existing studies from Medline published 1996 to present using keyword search for (“impact of COVID-19 on cancer”), (“COVID-19” OR “SARS-CoV-2”) AND (“cancer” OR “oncology”) AND (“chemotherapy” OR “immunotherapy”). Data from England demonstrate a substantial reduction in initiation of all types of systemic cancer therapies early in the pandemic, with recovery to normal levels by June 2020. There were noteworthy reductions in neoadjuvant therapy and non-curative chemotherapy, as well as immunotherapy. A report from Scotland indicated fewer attendances for systemic anticancer therapy in March to April 2020 compared to prior years. Population-based data from England and Northern Ireland revealed significant decreases in urgent referrals for chemotherapy and chemotherapy attendances at the onset of the COVID-19 pandemic. Retrospective studies of patients with cancer receiving intravenous anti-cancer therapy at New York hospitals found that around half of patients had treatment modifications. These reports contrast with findings from New Zealand, where the number of chemotherapy attendances did not change despite reductions in cancer registrations and diagnostic procedures in 2020. Survey-based reports suggest changes to standard therapy were instituted by cancer clinicians in Australia and overseas. However, the quality of this evidence is poor as it reflects views of respondents, not verified changes in treatment.

We found one systematic review of delays and disruptions to cancer health care during the COVID-19 pandemic. This identified 62 relevant studies, but none were of high methodological quality and few were related to changes to systemic cancer therapy. Again, many of the reports were based on surveys of staff or centres rather than primary data. This indicates an evidence gap in this area.

Added value of this study

To our knowledge, this is the first analysis of national, person-level data of cancer medicine use during the COVID-19 pandemic. Our Australian data allowed us to investigate whether specific recommendations from guidelines were applied and provides additional information about systemic cancer therapy not assessed in prior international studies. It is the first study to quantify use of growth factor support, anti-emetics, and change from parenteral to oral medicines. Data from England about systemic treatment initiation was limited to recently approved cancer medicines, which excludes a large proportion of cytotoxic regimens, whereas this report includes all government-subsidised systemic cancer therapy. Prior to this study there were no data about use of hormonal cancer therapies during the COVID-19 pandemic.

Implications of all the available evidence

This study provides high-quality evidence that at a national level, systemic cancer therapy changed minimally in Australia in the context of the COVID-19 pandemic. This was seen in New Zealand as well. This finding is unexpected given that other aspects of cancer care were temporarily disrupted and contrasts with findings in other countries. Both these countries have low incidence of SARS-CoV-2 infection and are well resourced. This is not the case for many other parts of the world, as pre-existing health disparities are further compounded by this virus. It remains a challenge globally to provide continuity of care for non-communicable diseases during the COVID-19 pandemic.

1. INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the virus that causes COVID-19) and the ensuing pandemic has affected health systems worldwide. People with cancer are particularly vulnerable to the effects of the COVID-19 pandemic. They are more than twice as likely to be infected with SARS-CoV-2 compared with the general population, probably relating to immunosuppressive effects of both cancer treatments and cancers themselves (especially haematological malignancies), as well as increased risk of nosocomial transmission due to frequent contact with the health system.[1,2] People with cancer who develop COVID-19 have poorer outcomes, with early reports indicating a 3.5-fold increase in the risk of invasive ventilation, intensive care unit admission or death, compared to people without cancer.[3] Moreover, observational studies of cancer patients with COVID-19 have reported mortality rates of 12-28%.[4-6]

Due to concerns about the increased risk of COVID-19 and excess morbidity and mortality among people with cancer, several guidelines were published between March and July 2020 providing advice on optimising management during the pandemic.[7-10] Australian and international guidance related to modifying cancer treatment to mitigate COVID-19-associated risk recommended: delaying adjuvant chemotherapy for patients with low risk of progression, considering treatment breaks for patients with low-volume and/or stable disease, transitioning from intravenous to oral anticancer agents, and expanding the use of supportive treatments to reduce the risk of treatment-associated toxicities (e.g. febrile neutropaenia and chemotherapy-induced vomiting) that might precipitate hospital admission.[7-11]

While there is evidence of reductions in cancer screening, diagnoses and surgeries in Australia during the COVID-19 pandemic, the impact on systemic cancer therapy is unknown.[12,13] Therefore, the aim of this study is to examine changes in systemic cancer therapy in Australia during the COVID-19 pandemic. Specifically, we describe changes in cancer medicine dispensing, initiation and discontinuation as well as changes in the use of supportive medicines.

2. METHODS

2.1. Study setting

Australia maintains a publicly funded, universal healthcare system entitling all citizens and eligible residents to subsidised prescription medicines, including cancer medicines, through the Pharmaceutical Benefits Scheme (PBS). The PBS subsidises cancer medicines that are dispensed in the community and delivered in public outpatient settings and private hospitals, and these records comprise the data used for the study. As the overwhelming majority of cancer treatment is administered in public outpatient clinics or private hospitals in Australia, our data contain a near-complete record of dispensed cancer medicines, nationally. This is a unique aspect of Australian medicines research, as many other countries with robust national or regional health data collections (e.g., the Nordic nations, Canada, UK) do not capture cancer medicines, which are administered in-hospital in those jurisdictions.[14-16]

2.1.1. COVID-19 in Australia

The Australian context for COVID-19 is illustrated in [Figure 1](#). The first wave of COVID-19 infections peaked in late March 2020, prompting travel and stay-at-home restrictions across Australia by the end of that month. Many restrictions were relaxed during May and remained that way for the balance of 2020 except for the

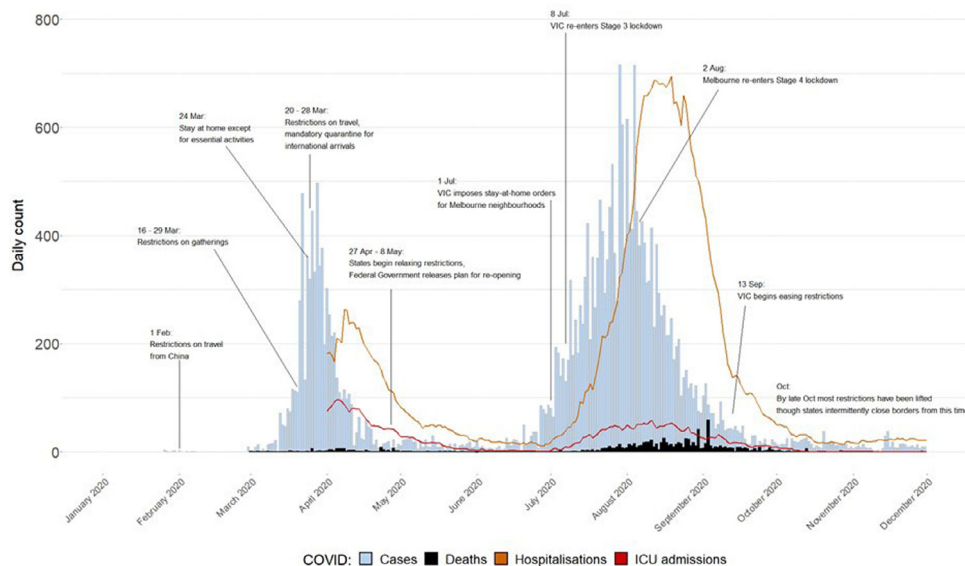


Figure 1. Australian government restrictions and daily number of COVID-19 cases, deaths and hospitalisations.[17-19]

State of Victoria. In July a second wave of COVID-19 infections predominantly affecting Victoria led the Victorian government to reimpose stay-at-home restrictions for the capital Melbourne, which extended to the whole of the State by August 2020.[17,18] As of 2 May 2021 there have been a cumulative 29,838 cases diagnosed in Australia (117 per 100,000 population) and 910 deaths.[19]

2.2. Data

To examine the impact of COVID-19 on PBS-subsidised cancer medicines, we undertook a population-based, observational study using all records of cancer medicines dispensed to a 10% sample of PBS-eligible people between 1 January 2017 through 31 December 2020. PBS dispensing claims are processed and recorded by Services Australia, which also maintains a dataset of these claims for a randomly-selected 10% sample of PBS-eligible Australians used for research and planning purposes. These de-identified, individual-level data include sex, year of birth, and records of dispensed prescription medicines (date of dispensing, medicine name and formulation (i.e., tablet, powder for infusion, etc.), the Australian State of dispensing).[20] The date of dispensing is offset by +/- 14 days but is the same for each individual. In Australia, once a medicine is PBS-subsidised the government bears the cost of the medicine. Private insurance will not provide reimbursement for medicines already subsidised through public programs, so it is unlikely that patients would access these medicines through other avenues. As such, these data likely capture the majority of cancer medicines dispensed in Australia during the study period.

2.3. Medicines of interest

This study reports on systemic cancer therapy (antineoplastic medicines and endocrine therapy) and supportive cancer medicines. We included all antineoplastic agents, as defined by the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification L01 publicly subsidised in Australia through the PBS (Supplementary Table A). We excluded oral formulations of methotrexate, cyclophosphamide and mercaptopurine as these are most often used for autoimmune conditions. To explore the possibility that oncologists attempted to transition patients from parenteral to oral chemotherapy (where possible) in response to the COVID-19 guidelines, we examined dispensings

of fluorouracil and capecitabine as a case study for this potential phenomenon. We included the following endocrine therapies in our analyses: anastrozole, bicalutamide, degarelix, exemestane, goserelin, letrozole, leuprorelin, tamoxifen, toremifene. Finally, we included non-antineoplastic medicines typically prescribed to support patients undergoing cancer treatment: filgrastim, lipegfilgrastim, pegfilgrastim, metoclopramide, ondansetron, palonosetron, granisetron, tropisetron, aprepitant, fosaprepitant, and combination netupitant/palonosetron.

2.4. Outcome measures and statistical analyses

We examined three cancer medicine utilisation measures—dispensings, initiations and discontinuations. We stratified our analyses by antineoplastic class (chemotherapy, immunotherapy, targeted therapy) and route of administration (oral, parenteral). Finally, to investigate the impact of the second outbreak in Victoria during July 2020 we stratified our analyses by State (Victoria, the rest of Australia).

2.4.1. Dispensings

We calculated monthly dispensing rates per 100,000 population using quarterly population estimates from the Australian Bureau of Statistics (ABS).[21] As our data are based on a 10% sample of the Australian population, we divided the ABS population estimates by 10. We examined monthly dispensing rates for all cancer medicines, fluorouracil and capecitabine, and all supportive medicines.

2.4.2. Initiations

For all cancer medicines, we defined treatment initiation as a dispensing of a cancer medicine where no cancer medicines were dispensed during the preceding 365 days. We used dispensing data from 2016 to determine initiations in 2017. We calculated monthly initiation rates per 100,000 population using quarterly population estimates from the ABS.

2.4.3. Discontinuations

We defined treatment discontinuation as a gap of 90 days between cancer medicines dispensings or following the last observed dispensing. We considered the date of discontinuation as the date

of the last dispensing before a ≥ 90 -day period with no dispensings, plus 30 days. We calculated the monthly discontinuation rate per 1,000 treated as the number of cancer medicine discontinuations in each month (numerator) over the number of people treated with cancer medicines during the previous month (denominator). For class-, and route-of-administration-specific rates we used the number of people in the specific group treated with the specific agent/formulation as the denominator for the rate. As a 90-day post-dispensing period is required to determine discontinuation, we examined discontinuations from 1 January 2017 until 30 September 2020.

2.4.4. Statistical analyses

To quantify changes in these utilisation measures compared with the counterfactual (i.e. predicted had pre-March 2020 trends in dispensings/initiations/discontinuations continued), we used interrupted time series analysis with autoregressive integrated moving average (ARIMA) models. Values in time series data are often correlated (commonly referred to as 'autocorrelation') and subject to seasonal variations. ARIMA models adjust for pre-existing trend, autocorrelation and seasonality in the data so that the resulting estimates are unbiased. For more information see the statistical supplement to this paper and our previous paper describing the use of ARIMA methodology for evaluating public health interventions [22]. We included variables representing temporary changes (only occurring during the month) for March 2020, April 2020, and July 2020; and a level shift (permanent change) from April 2020 through December 2020 in our ARIMA models. We modelled temporary changes in March and April as Australian COVID restrictions did not come into full effect until late March and the impacts may have carried over into April; and we modelled a temporary change in July 2020 to capture the impacts of the second outbreak in Victoria and subsequent lockdowns there. We modelled a permanent, level shift from April 2020 until the end of our study period to capture longer-term changes in patient and physician behaviours. We present the estimates from the full models (including all change variables) in Table 1. To produce easily interpretable figures we constructed our figures by extracting linear trends from models that only included significant change terms. Where all month and level terms were non-significant (e.g. no significant changes from March 2020), we extrapolated the pre-March 2020 trend to the end of the series for all figures.

All analyses were performed in R version 3.6.2 using the *forecast*[23] and *astsa*[24] packages.

2.5. Ethics and data access

Ethics approval for our study was granted by the NSW Population & Health Services Research Ethics Committee (approval number: 2013/11/494). Data access was granted by the Services Australia External Request Evaluation Committee (approval number: RMS1126). Direct access to the data and analytical files by other individuals or authorities is not permitted without the express permission of the approving human research ethics committees and data custodians.

2.6. Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3. RESULTS

Between January 2017 and December 2020, there were 1,011,255 cancer medicines (560,442 antineoplastic and 450,813 endocrine therapy dispensings) dispensed to 51,515 people (27,915

dispensed antineoplastics; 28,482 dispensed endocrine therapies). Prior to the COVID-19 pandemic in 2020, there was a background trend of increased cancer medicines dispensing over time, which may be related to the increases in cancer diagnoses and availability of cancer medicines over time (Figure 2). The most frequently dispensed antineoplastic medicines included fluorouracil (63,685, 11%), paclitaxel (35,098, 6%), and gemcitabine (23,202, 4%); the most frequently dispensed endocrine therapies were anastrozole (124,769, 27%), letrozole (118,087, 27%), and tamoxifen (86,429, 19%). Parenteral formulations comprised the majority of dispensings (454,096, 81%) and most patients dispensed a cancer medicine were 65 years or older (28,764, 55%).

3.1. Antineoplastic medicines

3.1.1. Dispensings

In the study period prior to March 2020, we observed a monthly mean of 454 dispensings of antineoplastic medicines/100,000 population (Table 1). Antineoplastic medicine dispensings did not decrease in the period March to December 2020, but there was a temporary increase of 39/100,000 (95% CI: 14 to 65/100,000) in antineoplastic medicine dispensings in March 2020 (Figure 2). There were no significant changes in chemotherapy dispensings (Figure 3), but we observed a temporary increase of 6/100,000 (2 to 10/100,000) in immunotherapy dispensings in March 2020, followed by a sustained increase of 11/100,000/month (3 to 18/100,000/month) from April 2020 (Figure 3). Dispensings of targeted therapy and all oral formulations increased temporarily in March and July 2020 (Figures 3 and 4). There were no changes in fluorouracil or capecitabine dispensings during the study period (Supplementary Figure 1).

There were no notable differences in dispensings of different classes of antineoplastic medicines between the State of Victoria, which was subject to the most restrictive lockdown measures, and the rest of Australia (Supplementary Figure 2).

3.1.2. Initiations

In March 2020, we observed an increase of 3/100,000 (1 to 5/100,000) in overall antineoplastic medicine initiations (Figure 2). Initiations of immunotherapy increased temporarily in March and April 2020, followed by a small, sustained increase of 1/100,000/month (0 to 2/100,000) (Figure 3). There was a temporary decrease in chemotherapy initiation of -2/100,000 (-4 to -1/100,000) in April 2020.

3.1.3. Discontinuations

Before March 2020, the mean monthly discontinuation rate was 144 discontinuations/1,000 people treated with antineoplastic medicines (Table 1). In April 2020, there was a temporary increase in antineoplastic medicine discontinuations of 35/1,000 (20 to 51/1,000) (Figure 2), and temporary increases in discontinuations of cytotoxic chemotherapy, and both oral and parenteral antineoplastic medicines (Figures 3 and 4).

3.2. Endocrine therapy

Dispensings of endocrine therapy increased temporarily by 51/100,000 population (33 to 68/100,000) in March 2020 (Figure 5). This was followed by a sustained decrease in endocrine therapy dispensings from April onwards, punctuated by a small increase of 17/100,000 (6 to 27/100,000) in July 2020. There was a temporary increase in endocrine therapy discontinuations in April 2020, but no changes in endocrine therapy initiation (Table 1).

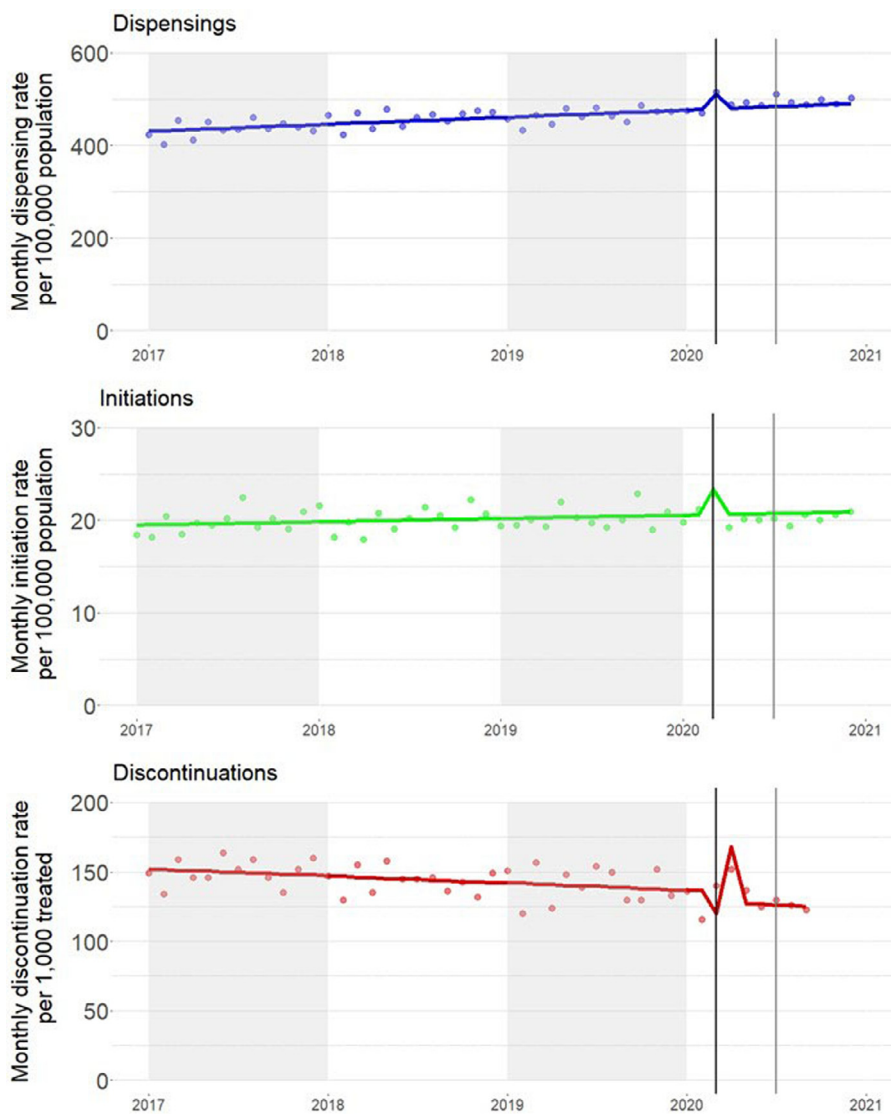


Figure 2. Interrupted time series of monthly dispensing, initiation and discontinuations of all antineoplastic (L01) medicines. Solid line indicates the fitted trend; points the observed series. Black line indicates March 2020, grey line indicates July 2020.

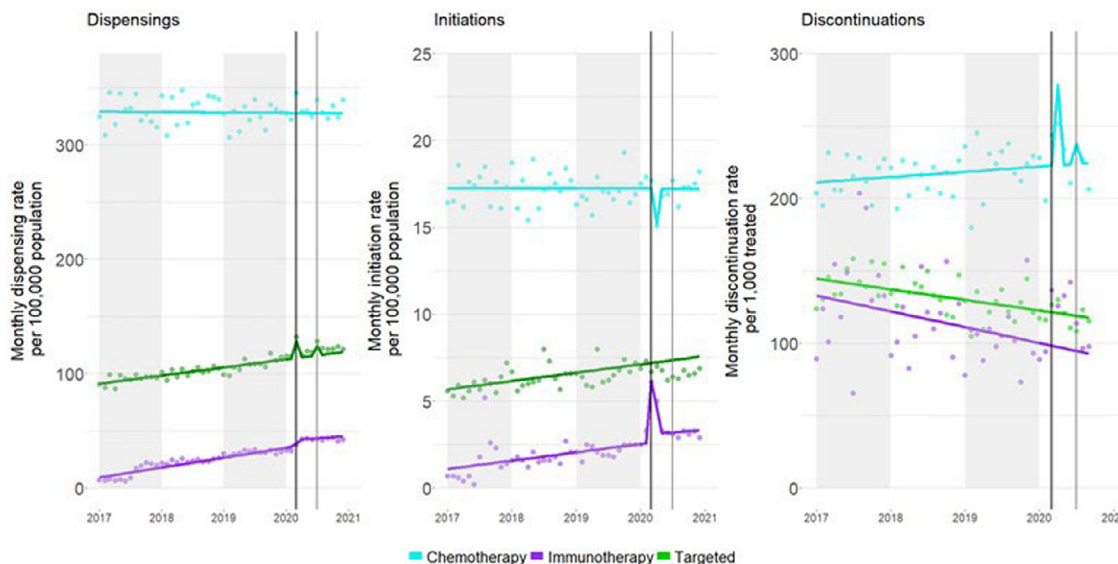


Figure 3. Interrupted time series of monthly dispensing, initiation and discontinuations of antineoplastic (L01) medicines, by class of medicines (cytotoxic chemotherapy, immunotherapy and targeted therapy). Solid line indicates the fitted trend; points the observed series. Black line indicates March 2020, grey line indicates July 2020.

Table 1

Estimated changes in monthly dispensings, initiations, and discontinuations of antineoplastic medicines, endocrine therapy and supportive medicines between March – December 2020 relative to historical trends.

		Temporary change: March 2020	Temporary change: April 2020	Temporary change: July 2020	Level change: April-Dec 2020
	Monthly mean rate per 100,000 prior to March 2020	Rate per 100,000 (95% CI)	Rate per 100,000 (95% CI)	Rate per 100,000 (95% CI)	Rate per 100,000 (95% CI)
Antineoplastic medicines (L01)					
Dispensings					
Overall	454	39 (14 to 65)	2 (-25 to 27)	19 (-3 to 41)	16(-8 to 40)
Chemotherapy	329	16 (-1 to 34)	8 (-11 to 27)	4 (-15 to 23)	2 (-5 to 9)
Immunotherapy	23	6 (2 to 10)	0 (-4 to 4)	1 (-3 to 4)	11 (3 to 18)
Targeted therapy	102	17 (10 to 24)	-2 (-8 to 4)	8 (2 to 14)	3 (-2 to 7)
Oral formulations	85	21 (15 to 26)	-4 (-10 to 2)	8 (3 to 13)	-3 (-9 to 4)
Parenteral formulations	370	18 (-2 to 37)	16 (-5 to 36)	3 (-17 to 22)	14 (2 to 26)
Initiations					
Overall	20	3 (1 to 5)	-1 (-3 to 1)	0 (-2 to 2)	0 (-1 to 1)
Chemotherapy	17	1 (-1 to 2)	-2 (-4 to -1)	0 (-2 to 2)	0 (-1 to 0)
Immunotherapy	2	4 (2 to 5)	2 (0 to 3)	0 (-1 to 1)	1 (0 to 2)
Targeted therapy	6	0 (-1 to 1)	0 (-1 to 2)	0 (-1 to 1)	0 (-1 to 1)
Oral formulations	7	1 (-1 to 2)	1 (0 to 2)	0 (-1 to 2)	0 (-1 to 0)
Parenteral formulations	17	3 (1 to 5)	-2 (-4 to 1)	-1 (-3 to 1)	0 (0 to 1)
Discontinuations*					
Overall	144	-11 (-24 to 1)	35 (20 to 51)	-2 (-19 to 15)	-8 (-14 to -3)
Chemotherapy	216	7 (-6 to 19)	52 (38 to 66)	20 (6 to 34)	-4 (-10 to 1)
Immunotherapy	116	21 (-36 to 78)	8 (-55 to 71)	-4 (-67 to 59)	1 (-28 to 31)
Targeted therapy	133	3 (-19 to 26)	13 (-10 to 36)	-9(-31 to 13)	-6 (-23 to 11)
Oral formulations	151	-3 (-24 to 19)	52 (29 to 75)	-1 (-23 to 21)	-10 (-23 to 3)
Parenteral formulations	171	-7 (-26 to 12)	30 (7 to 53)	-8 (-32 to 16)	-11 (-20 to -2)
Endocrine therapies (L02)					
Dispensings					
Overall	301	51 (33 to 68)	-17 (-33 to -2)	17 (6 to 27)	-34 (-52 to -15)
Oral formulations	253	35 (23 to 47)	-10 (-22 to 2)	11 (2 to 19)	-44 (-64 to -23)
Parenteral formulations	48	5 (3 to 7)	-3 (-5 to -1)	1 (-1 to 3)	-1 (-2 to -1)
Initiations					
Overall	15	2 (-1 to 4)	-1 (-4 to 1)	0 (-2 to 3)	0 (-1 to 2)
Oral formulations	11	1 (-1 to 2)	-2 (-4 to 0)	0 (-2 to 1)	1 (0 to 2)
Parenteral formulations	6	1 (0 to 2)	0 (-1 to 1)	0 (-1 to 1)	0 (-1 to 1)
Discontinuations*					
Overall	112	0 (-9 to 9)	34 (24 to 43)	-3 (-10 to 4)	-3 (-14 to 8)
Oral formulations	78	4 (-1 to 11)	41 (35 to 47)	-3 (-7 to 2)	1 (-10 to 11)
Parenteral formulations	381	-36 (-81 to 9)	32 (-20 to 84)	-26 (-78 to 26)	3 (-21 to 28)
Supportive medicines					
Dispensings					
Overall	531	-31 (-62 to 0)	13 (-17 to 44)	11 (-10 to 33)	-60 (-113 to -7)
Granulocyte-colony stimulating factors**	22	5 (1 to 8)	3 (-1 to 7)	0 (-3 to 3)	4 (0 to 9)
Metoclopramide	289	-8 (-26 to 9)	1 (-16 to 19)	5 (-10 to 20)	-14 (-34 to 6)
Ondansetron	131	-29 (-43 to -14)	1 (-13 to 15)	8 (-2 to 18)	-42 (-68 to -18)
Other serotonin antagonists†	54	2 (-4 to 8)	2 (-4 to 9)	-2 (-7 to 3)	0 (-11 to 11)
Netupitant & palonosetron	25	3 (-2 to 8)	-1 (-5 to 4)	-1 (-4 to 2)	3 (-7 to 13))
Other neurokinin receptor antagonists‡	10	2 (-2 to 6)	1 (-3 to 6)	0 (-3 to 3)	1 (-7 to 8)

* Estimates for discontinuations are presented per 1,000 instead of per 100,000

** Filgrastim, lipegfilgrastim, pegfilgrastim

† Granisetron, palonosetron, and tropisetron

‡ Aprepitant and fosaprepitant

3.3. Supportive medicines

Dispensing of granulocyte-colony stimulating factors (G-CSF; filgrastim, lipegfilgrastim and pegfilgrastim) increased in March 2020, preceding a sustained increase of 4/100,000 (0 to 9/100,000) from April 2020 onwards (Figure 6). Dispensings of ondansetron decreased by -29/100,000 (-43 to -14/100,000) in March 2020, followed by a sustained decrease of -42 (-68 to -18/100,000/month) from April 2020 onwards. There were no changes in dispensings of other antiemetics, including metoclopramide, neurokinin receptor antagonists and other serotonin antagonists (Table 1).

4. DISCUSSION

This population-based, observational study demonstrated that, overall, systemic cancer treatment in Australia was not substan-

tially impacted by COVID-19. At the onset of the pandemic in March 2020, we observed temporary changes in antineoplastic medicine dispensings, chemotherapy initiations, and antineoplastic medicine discontinuations. While some changes persisted through the end of the year, the changes were small and none of them suggest the widespread adoption of COVID-19-related guideline recommendations, such as sustained reductions in anti-cancer treatment initiation, ongoing higher rates of treatment discontinuation, transition from intravenous to oral medicines, or increased use of antiemetics.

The minimal changes to systemic therapy we observed likely reflect the relatively low number of COVID-19 cases in Australia. New Zealand also experienced low rates of COVID-19 infection and, similar to Australia, there were no obvious reductions in intravenous chemotherapy administration there.[25] By contrast, the number of monthly registrations for new systemic anticancer treatments

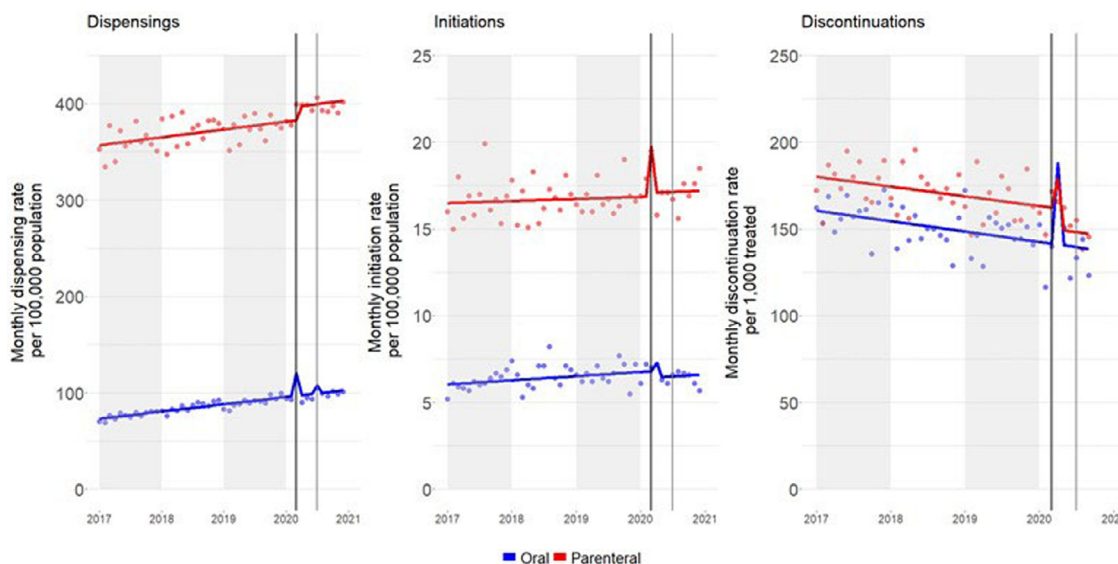


Figure 4. Interrupted time series of monthly dispensing, initiation and discontinuations of antineoplastic (L01) medicines, by route of administration. Solid line indicates the fitted trend; points the observed series. Black line indicates March 2020, grey line indicates July 2020.

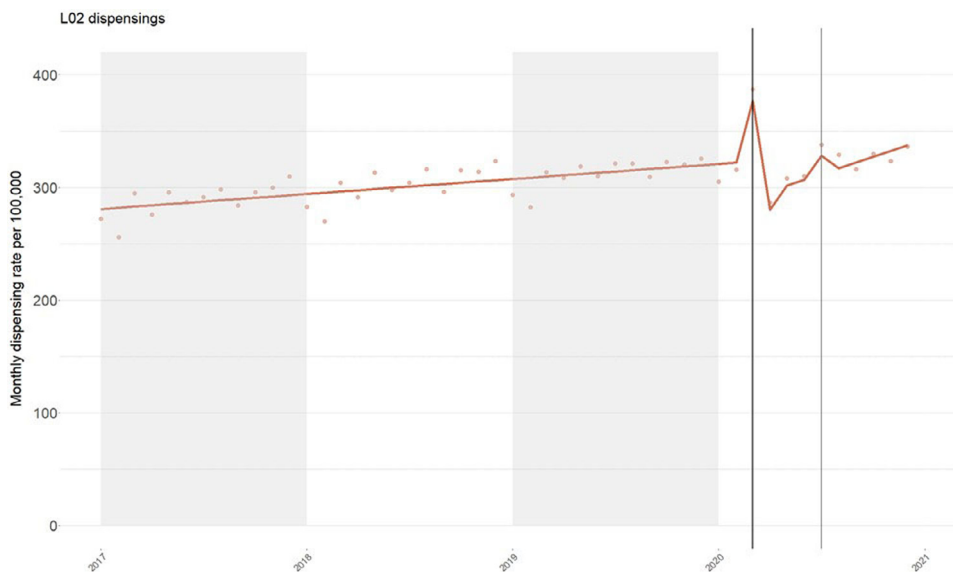


Figure 5. Interrupted time series of monthly dispensings of endocrine therapy (L02). Solid line indicates the fitted trend; points the observed series. Black line indicates March 2020, grey line indicates July 2020.

fell by 32% in England in April 2020 compared to the pre-COVID-19 comparison period.[26] In the same region, weekly attendances for systemic cancer therapy fell by approximately 30% in England, Northern Ireland and Scotland.[27,28] Single-centre studies from the US report that around half of patients on chemotherapy had treatment modifications in February to April 2020.[29,30] A systematic review found evidence of significant delays and disruptions to cancer care worldwide during the COVID-19 pandemic.[31] Apart from New Zealand data, there have been few studies of changes to systemic cancer therapy use in the Western Pacific region.[25,31] Institution-based studies from Western Pacific nations such as China, Japan and Philippines, with higher rates of COVID-19 infection than Australia, report that systemic cancer therapy was delayed in up to 50% of patients.[32-34] However, based on early reports it appears that countries with low rates of infection, like Australia and New Zealand, were largely able to continue to deliver routine systemic cancer treatment, while coun-

tries with higher infection rates were more likely to modify cancer care.

Temporal factors may also have contributed to the stability in cancer medicines use observed in this study. First, local COVID-19 guidelines were initially endorsed in March 2020 before formal publication in May to June 2020.[7,8] Therefore, there may have been a delay associated with dissemination and adoption of clinical guidelines, such that any changes in practice may not be captured by our study period. Second, there is usually several weeks to months between cancer screening or presentation with cancer-related symptoms and subsequent systemic therapy initiation. In Australia we observed the temporary suspension of the national breast cancer screening program, an approximate one-third decrease in the number of monthly breast cancer-related surgeries in May 2020, and an estimated 5,500 fewer new cancer diagnoses in Victoria (Australia's second most populous state) than predicted from 1 April to 15 October 2020.[12,13] However, the impact of

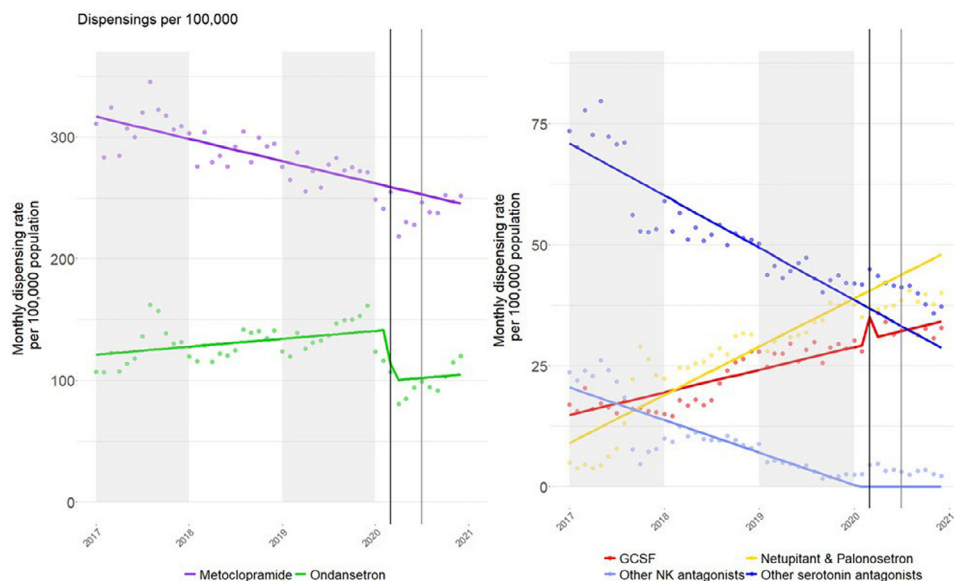


Figure 6. Interrupted time series of dispensings of supportive medicines. Solid line indicates the fitted trend; points the observed series. Black line indicates March 2020, grey line indicates July 2020. G-CSF granulocyte-colony stimulating factor, NK neurokinin.

screening and diagnoses delays may not yet be evident in our results due to the typical timeframe between cancer diagnosis and treatment initiation.

Despite the overall stability in cancer medicine use and the small changes observed, our findings suggest some adjustments to clinical care during the pandemic. In April 2020, we found a temporary decrease in chemotherapy initiations. This may have arisen from recognition of increased risks associated with chemotherapy-related immunosuppression and hospital attendances for intravenous chemotherapy administration. We also found a temporary increase in discontinuations of antineoplastic medicines during April 2020, predominantly driven by cytotoxic chemotherapy, which may reflect the increased adoption of chemotherapy treatment breaks during the first wave of COVID-19 infections. On the other hand, we did not see evidence of patients switching from intravenous 5-fluorouracil to oral capecitabine, as recommended by some guidelines.[7-9] This may be because 5-fluorouracil is often used in combination with intravenous chemotherapies (e.g. oxaliplatin or irinotecan) that have no oral equivalents, so changing from 5-fluorouracil to capecitabine would not have eliminated the need for intravenous treatment for patients receiving combination chemotherapy.

Some of the observed changes in systemic cancer therapy use were likely unrelated to COVID-19 cancer guidelines. The temporary and sustained increases in immunotherapy dispensings and initiations from March 2020 was likely related to new indications for government-subsidised immune checkpoint inhibitors that were added to the PBS around the same time. For example, from 1 March 2020 nivolumab was publicly subsidised for the adjuvant treatment of melanoma; durvalumab was subsidised as consolidation therapy for patients following chemoradiation for locally advanced non-small cell lung cancer; and atezolizumab was subsidised for use in combination with chemotherapy for extensive-stage small cell lung cancer. These newly-subsidised indications are more likely the cause of the changes we observed than COVID-19.

The increase in the use of G-CSF aligns with recommendations to adopt a lower threshold for prophylactic use of growth factor support to reduce the risk of treatment-related neutropaenic infection.[7,8,10,35] While anti-emetic use did not increase, there was less dispensing of the short-acting oral serotonin antagonist on-

dansetron, which is PBS-listed for the treatment of chemotherapy- and radiotherapy-induced nausea, but which is frequently used off-label for other conditions, such as infective gastroenteritis. This reduction in ondansetron dispensing may be related to fewer cases of infective gastroenteritis reported in Australia in 2020 compared to preceding years, likely secondary to COVID-19-related social distancing measures.[36-38]

A strength of our study is its use of a large, nationally representative dataset comprising PBS dispensing records for 10% of the Australian population to investigate potential changes in cancer medicines use during the COVID-19 pandemic. Generalisations around the impacts of COVID-19 are challenging, but our findings may generalise to other similar countries with similarly low numbers of COVID-19 cases. Our study is unique in its capacity to capture all government-subsidised anti-cancer medicines, in contrast to existing studies that have only captured recently approved medicines (thereby excluding most cytotoxic chemotherapy), or only reported on treatment attendances.[25-28] The PBS funds all medicines dispensed through community pharmacies and hospital outpatient oncology units. The overwhelming majority of systemic cancer therapy is administered in hospital outpatient oncology units, so our data provides a comprehensive picture of treatment patterns in Australia and across different treatment delivery settings. The main limitation of our study is its lack of clinical data and indications for which cancer medicines were dispensed. We are unable to determine changes in systemic cancer therapy according to tumour type or stage, or whether changes occurred in response to adverse events. Our study only includes medicines that are government-subsidised through the PBS and does not capture patients receiving cancer medicines through other avenues, such as clinical trials and compassionate access schemes, although this number is likely to be relatively small. The PBS dispensing records comprising our data are consistently offset by up to +/- 14 days for each patient to protect privacy. This may have resulted in some of our study outcomes shifting from the true month in which they occurred to the preceding or following month in the data. We have only reported on data for the first ten months of the COVID-19 pandemic and a longer data series would be required to study any longer term changes to cancer medicines use, such as the impact of delayed or missed cancer diagnoses. Finally, we have carried out multiple statistical tests in the course of our analyses and it is the-

oretically possible that some of the significant results we observed were due to chance.

5. CONCLUSION

In Australia, there were minimal changes to cancer medicines relating during the COVID-19 pandemic in 2020. This may be due to the relatively low rates of COVID-19 in Australia. Despite concerns about the potential for COVID-19 to compromise the clinical care of patients with cancer, effective control of community transmission appears to have mitigated the impact of COVID-19 on cancer medicines use in Australia.

Declaration of Competing Interest

The authors declare no conflicts of interest relevant to the submitted work.

SAP is a member of the Drug Utilisation Sub Committee of the Pharmaceutical Benefits Advisory Committee. The views expressed in this paper do not represent those of the Committee.

The Centre for Big Data Research in Health, UNSW Sydney, has received funding from AbbVie Australia to conduct research, unrelated to this study. AbbVie did not have any knowledge of, or involvement in, the present study.

Authors' Contributions

MT, BD and SAP created the initial concept and study design. BD was responsible for data analysis. MT and BD wrote the original draft. MT, BD, MA, AS and SAP were involved in data interpretation, reviewing and editing the manuscript, and the decision to submit for publication.

Acknowledgments

This research is supported by the National Health and Medical Research Council Centre of Research Excellence in Medicines Intelligence (ID: 1196900). MT is supported by an Australian Government Research Training Program Scholarship, a National Health and Medical Research Council Postgraduate Research Scholarship (ID: 1151479), a National Breast Cancer Foundation Postgraduate Scholarship Top-Up (ID: DS-18-01), and a Translational Cancer Research Network Clinical PhD Scholarship Top-Up award, supported by the Cancer Institute NSW. AS is supported by a National Health and Medical Research Council Early Career Fellowship (ID: 1158763).

We thank the Australian Government Services Australia for providing the data and Melisa Litchfield for assisting with data access and ethics approval.

Data Sharing

The PBS and MBS claims data are publicly available at <https://www.pbs.gov.au/info/statistics/dos-and-dop/dos-and-dop> and http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp. Access to the 10% PBS sample was granted by the Services Australia External Request Evaluation Committee (approval number: RMS1128). Direct access to these data and analytical files to other individuals or authorities is not permitted without the express permission of the approving human research ethics committees and data custodians.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.lanwpc.2021.100226](https://doi.org/10.1016/j.lanwpc.2021.100226).

REFERENCES

- [1] Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020;323(11):1061–9.
- [2] Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. *JAMA oncology* 2020;6(7):1108–10.
- [3] Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *The Lancet Oncology* 2020;21(3):335–7.
- [4] Lee LYW, Cazier J-B, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *The Lancet* 2020;395(10241):1919–26.
- [5] Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *The Lancet* 2020;395(10241):1907–18.
- [6] Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. *Nature Medicine* 2020;26(8):1218–23.
- [7] Segelov E, Underhill C, Prenen H, et al. Practical considerations for treating patients with cancer in the COVID-19 pandemic. *JCO Oncology Practice* 2020;16(8):467–82.
- [8] Weinkove R, McQuilten ZK, Adler J, et al. Managing haematology and oncology patients during the COVID-19 pandemic: interim consensus guidance. *Med J Aust* 2020;212(10):481–9.
- [9] HO Al-Shamsi, Alhazzani W, Alhurairi A, et al. A Practical Approach to the Management of Cancer Patients During the Novel Coronavirus Disease 2019 (COVID-19) Pandemic: An International Collaborative Group. *Oncologist* 2020;25(6):e936–ee45.
- [10] Curigliano G, Banerjee S, Cervantes A, et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Annals of Oncology* 2020;31(10):1320–35.
- [11] Schrag D, Hershman DL, Basch EJ. Oncology practice during the COVID-19 pandemic. *JAMA* 2020;323(20):2005–6.
- [12] Cancer Australia. National and jurisdictional data on the impact of COVID-19 on medical services and procedures in Australia: Breast, colorectal, lung, prostate and skin cancers. Cancer Australia. Surry Hills. NSW 2020.
- [13] Te Marvelde L, Wolfe R, McArthur G, Blake LA, Evans SM. Decline in cancer pathology notifications during the 2020 COVID-19-related restrictions in Victoria. *The Medical journal of Australia* 2021.
- [14] Suissa S, Henry D, Caetano P, et al. CNODES: the Canadian network for observational drug effect studies 2012;6(4):e134.
- [15] Clinical Practice Research Datalink. CPRD Linked Data. 2021. <https://www.cprd.com/linked-data>. (Accessed 5 June 2021).
- [16] Wettermark B, Zoëga H, Furu K, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research—a literature review. *Pharmacoepidemiology and Drug Safety* 2013;22(7):691–9.
- [17] COVID-19 National Incident Room Surveillance Team. COVID-19 Australia: Epidemiology Report 36: Reporting period ending 28 February 2021. Communicable diseases intelligence 2021;45.
- [18] Higgsinson S, Milovanovic K, Gillespie J, et al. COVID-19: The need for an Australian economic pandemic response plan. *Health Policy and Technology* 2020;9(4):488–502.
- [19] Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. Coronavirus Pandemic (COVID-19). 2020. <https://ourworldindata.org/coronavirus> (Accessed 27 April 2021).
- [20] Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC Res Notes* 2015;8 634–.
- [21] Australian Bureau of Statistics. ABS.State beta. 2021. <http://stat.data.abs.gov.au/#> (Accessed 31 March 2021).
- [22] Schaffer AL, Dobbins TA, Pearson S-A. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. *BMC Medical Research Methodology* 2021;21(1):58.
- [23] Hyndman RJ, Athanasopoulos G, Bergmeir C, et al. forecast: Forecasting functions for time series and linear models. 2018. <http://pkg.robjhyndman.com/forecast>.
- [24] Stoffer D. aatsa: Applied statistical time series analysis. 2014. <https://CRAN.R-project.org/package=aatsa>.
- [25] Gurney JK, Millar E, Dunn A, et al. The impact of the COVID-19 pandemic on cancer diagnosis and service access in New Zealand—a country pursuing COVID-19 elimination. *The Lancet Regional Health - Western Pacific* 2021;10:100127.
- [26] Clark JJ, Dwyer D, Pinwill N, Clark P, Johnson P, Hackshaw A. The effect of clinical decision making for initiation of systemic anticancer treatments in response to the COVID-19 pandemic in England: a retrospective analysis. *The Lancet Oncology* 2020.
- [27] Lai AG, Paisea L, Banerjee A, et al. Estimated impact of the COVID-19 pandemic on cancer services and excess 1-year mortality in people with cancer and multimorbidity: near real-time data on cancer care, cancer deaths and a population-based cohort study. *BMJ Open* 2020;10(11):e043828.
- [28] Baxter MA, Murphy J, Cameron D, et al. The impact of COVID-19 on systemic anticancer treatment delivery in Scotland. *British Journal of Cancer* 2021;124(8):1353–6.
- [29] Lin DD, Meghal T, Murthy P, et al. Chemotherapy Treatment Modifications During the COVID-19 Outbreak at a Community Cancer Center in New York City. *JCO Global Oncology* 2020;6:1298–305.

- [30] Satish T, Raghunathan R, Prigoff JG, et al. Care Delivery Impact of the COVID-19 Pandemic on Breast Cancer Care. *JCO Oncology Practice* 2021 OP.20.01062.
- [31] Riera R, Bagattini AM, Pacheco RL, Pachito DV, Roitberg F, Ilbawi AJGO. Delays and Disruptions in Cancer Health Care Due to COVID-19 Pandemic: Systematic Review. *JCO Global Oncology* 2021;7(1):311–23.
- [32] Sun L, Xu Y, Zhang T, Yang Y. Impact of the COVID-19 outbreak on adjuvant chemotherapy for patients with stage II or III colon cancer: experiences from a multicentre clinical trial in China. *Current oncology (Toronto, Ont)* 2020;27(3):159–62.
- [33] Fujita K, Ito T, Saito Z, Kanai O, Nakatani K, Mio T. Impact of COVID-19 pandemic on lung cancer treatment scheduling. *Thoracic Cancer* 2020;11(10):2983–6.
- [34] Panday JG, Maaño O, Balolong-Garcia JC, Datukan JTY. Risk factors and clinical outcomes of systemic cancer treatment delays in Filipino patients with solid tumor malignancy during the COVID-19 pandemic: A single tertiary center study. *Cancer reports (Hoboken, NJ)* 2021:e1426.
- [35] El-Shakankery KH, Kefas J, Crusz SM. Caring for our cancer patients in the wake of COVID-19. *British journal of cancer* 2020;123(1):3–4.
- [36] Bright A, Glynn-Robinson A-J, Kane S, Wright R, Saul N. The effect of COVID-19 public health measures on nationally notifiable diseases in Australia: preliminary analysis. *Communicable Diseases Intelligence* 2020(2018):44.
- [37] Bruggink LD, Garcia-Clapes A, Tran T, Druce JD, Thorley BR. Decreased incidence of enterovirus and norovirus infections during the COVID-19 pandemic. *Commun Dis Intell* 2020.
- [38] Adegbija O, Walker J, Smoll N, Khan A, Graham J, Khandaker G. Notifiable diseases after implementation of COVID-19 public health prevention measures in Central Queensland, Australia. *Commun Dis Intell* 2021.