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Research

Retrospective comparison of Australia's Pharmaceutical Benefits Scheme claims data with prescription data in HER2-positive early breast cancer patients, 2008–2012

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Key points

- Dispensing claims are a robust proxy for prescription data to describe medicine use in patients with HER2-positive breast cancer
- In patients with complete ascertainment of dispensing claims, treatment protocols and durations of treatment derived from dispensing claims are consistent with medicines prescribed and administered; but dispensing claims underestimate the number of treatment cycles

Abstract

Objectives: Dispensing claims are used increasingly to investigate the real-world use and impact of prescribed medicines. Claims databases, established for payment purposes, lack clinical data and only capture prescriptions for which insurers pay a contribution. We compare Australia's Pharmaceutical Benefits Scheme (PBS) dispensing claims of HER2-positive early breast cancer patients with medicines prescribed and administered to determine the accuracy of dispensing data to identify treatment protocols, number of treatment cycles and durations of therapy.

Method: Our cohort comprised 110 female HER2-positive early breast cancer patients who started treatment at four cancer centres in New South Wales, Australia, between 2008 and 2011. Patients consented to retrospective medical chart audit and linkage to PBS claims data. We constructed protocols from prescribing and dispensing records independently, based on the timing of trastuzumab and cytotoxic treatments; and estimated the median number of treatment cycles and duration of therapy by protocol.

Results: Patients' median age was 53 years (range 21–86). Two chemotherapy protocols accounted for 90% of chemotherapy protocols: doxorubicin and cyclophosphamide followed by a paclitaxel or docetaxel and trastuzumab (known as ACTH; 58.2%) and trastuzumab with docetaxel, carboplatin and trastuzumab (known as TCH; 31.2%). Seventy-six patients (69.1%) were assigned the same protocols based on prescribing and claims data. Twenty-six of the protocols that did not match were due to the absence of cyclophosphamide in PBS data because it falls below the patient copayment for general PBS beneficiaries. Compared with prescription data,

- Recent policy changes will lead to more accurate measurement of cancer treatment in Australia's Pharmaceutical Benefits Scheme dispensing claims

the number of treatment cycles was underestimated in dispensing data (30 vs 44 for ACTH and 26.5 vs 29 for TCH); however, median durations of therapy were well matched (422 vs 442 days for ACTH and 368 vs 367 for TCH).

Conclusions: PBS dispensing data provide an alternative option to prescription data for estimating cancer medicine use. Recent changes to PBS data capture that include all medicines costing less than the copayment data will strengthen the capacity of PBS data to reflect prescribing practice in all patients, including treatment protocols and duration of therapy in patients with complete ascertainment of PBS dispensing history.

Introduction

Postmarket surveillance activities rely increasingly on routine data to quantify population-level benefits and risks of prescribed medicines.[1,2] Although analyses based on routine data collections such as dispensing claims are time and cost effective, they have limitations.[3] Studies assessing the accuracy of routinely collected data to reflect real-world practices are not commonplace, but they are important to ensure the accuracy of the assumptions made when using these data.[4]

Anticancer medicines account for an increasing proportion of Australia's Pharmaceutical Benefits Scheme (PBS) spend, yet to date there are very few Australian postmarket surveillance studies focused on cancer medicines.[5] The purpose of this study is to compare the PBS dispensing claims of human epidermal growth factor receptor 2 (HER2)–positive early breast cancer patients, with clinic prescriptions to determine the accuracy of dispensing data in identifying treatment protocols, number of treatment cycles and durations of therapy.

Between 15% and 25% of patients diagnosed with breast cancer overexpress HER2.[6,7] Trastuzumab is a monoclonal antibody targeting the HER2 receptor and, when used with chemotherapy, reduces recurrence rates and improves survival in patients with HER2-positive breast cancer. Trastuzumab with chemotherapy is considered standard of care and is subsidised by the PBS for 52 weeks for patients with histologically proven HER2-positive early breast cancer.

Methods

Cohort selection

We identified early stage (nonmetastatic) breast cancer patients by reviewing pathology results, oncology databases and medical charts at four hospitals in New South Wales (NSW), Australia, that provide services to approximately 800 000 people in South Eastern Sydney (11.7% of the total NSW population). Eligible patients were those with a histopathological diagnosis of nonmetastatic HER2-positive breast cancer as determined by a positive HER2 in situ hybridisation gene test. We included patients who were diagnosed between January 2008 and June 2012, were receiving trastuzumab therapy and were alive at the time of recruitment (2011–2012). These patients were eligible for PBS-subsidised trastuzumab treatment following surgery (adjuvant treatment). We excluded patients receiving chemotherapy and trastuzumab before surgery (neoadjuvant treatment) and patients with metastatic disease.

Patient consent

We sought individual informed consent from all eligible patients to link their PBS dispensing history to their treatment records. We contacted treating oncologists to establish that patients were eligible for inclusion and that contact about the study would not cause undue stress. We mailed patients study documentation, and those who chose to participate returned the signed consent forms directly to us. Treating oncologists were not told whether patients participated in the study.

Data

We undertook a pilot study to refine our data collection tool and establish the best sources of information about the medicines accessed by patients. We found medication charts were the most appropriate point of reference to determine the prescribed intravenous medications administered to patients. However, we found that the name and strength of oral hormone therapies were recorded in the medical notes.

For the main study, we retrospectively extracted each anticancer medicine (including trastuzumab and chemotherapy) prescribed and administered to consenting patients and oral medications referred to in the medication charts irrespective of whether the medicines were PBS funded, self-funded, used off label, or administered as part of a clinical trial (Supplementary Table 1, available from: http://handle.unsw.edu.au/1959.4/unsworks_48034). We collected this data for each patient from the date of the first HER2 breast cancer pathology report until trastuzumab cessation or until the study census date (30 June 2012), whichever came first.

We obtained the retrospective PBS records of consenting patients from January 2008 to June 2012 from the Australian Government Department of Human Services (DHS), the data custodian for the PBS. We used Anatomical Therapeutic Chemical (ATC) codes and PBS item codes to identify anticancer

treatments within these records (Supplementary Table 1, available from: http://handle.unsw.edu.au/1959.4/unsworks_48034).[8,9] PBS-listed medicines are subsidised by the Australian government, with patients paying a copayment when the cost of a medication is above a specific threshold. Historically, medicines costing less than the patient copayment were not ascertained in the collection, meaning that low-cost medicines dispensed to beneficiaries with the highest patient copayment threshold (general beneficiaries) were underascertained. This did not impact on the capture of medicines dispensed to concessional beneficiaries as they have lower copayment thresholds. Due to regulatory changes, all PBS-listed drugs, including those below the copayment are captured in the PBS records from April 2012.[10,11]

Statistical analysis

First, we classified patients according to chemotherapy and hormone therapy received using prescribing and dispensing data independently, to construct treatment protocols based on evidence based guidelines. We used Australia's eviQ guidelines which provide treatment protocols based on evidence from clinical trial data.[12-18] In prescription data, we classified the treatment protocols according to the individual medicines prescribed and administered. In dispensing data, we first identified the trastuzumab treatment period as the date of first dispensing to the date of last trastuzumab dispensing, plus 30 days.[19] We searched for other anticancer therapies (chemotherapy and hormone therapy) as per eviQ evidence based protocols[18] that were dispensed in the period 90 days before the commencement of trastuzumab (to ensure we captured all medicines dispensed until the last day of trastuzumab dispensing plus 30 days (a standard approach to estimate treatment exposure in pharmacoepidemiological studies).[5]

After assigning treatment protocols, we estimated the number of trastuzumab and cytotoxic treatments, and duration of anticancer treatment, by protocol in prescribing and dispensing data for the subset of individuals in whom the protocol assignment matched between prescribing and dispensing data. We calculated the number of treatments in prescription data by counting the number of medication entries signed on administration charts and the number of treatments in dispensing data by counting the number of dispensings of a drug in PBS claims. In prescription and dispensing data, we defined duration of treatment as the time from the first date of administration/dispensing of the medicine in question until the date of last administration/dispensing of that same medicine, plus 30 days.

We defined periods between administration/dispensing of greater than 90 days as a break in treatment. We defined treatment end date as 30 days from the last administration/dispensing before the 90-day gap. We censored our duration calculations at 30 June 2012 because both datasets terminated on this date. We were unable to compare these outcomes for hormone treatments because there was insufficient information in the medical notes to derive the estimates.

Ethical and data access approval

This study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee. The DHS External Review Evaluation Committee approved access to the PBS dispensing claims.

Results

We identified 203 patients with HER2-positive early breast cancer, 39 of whom did not receive any trastuzumab therapy; we were also advised by the treating oncologist not to contact 12 patients. We contacted 152 patients to participate in the study and 112 patients agreed (response rate of 74%). The DHS supplied the PBS records of 110 patients, and those patients comprised our analytical cohort.

All patients were female with a median age of 53 years (range 21 to 86 years); 34.5% had stage 1 disease, 42.7% had stage 2 and 22.7% had stage 3 disease. Of all tumours, 77.3% were grade 3 and 60.0% were oestrogen-receptor positive. Approximately two-thirds of the cohort were general PBS beneficiaries for the entire study period (Table 1). The characteristics of the study cohort (N = 110) were similar to the entire group of patients identified with HER2-positive early breast cancer (N = 164).

Classification of treatment protocols derived from prescribing and dispensing data

Using prescribing data, we identified six unique chemotherapy protocols, five of which were consistent with eViQ protocols.[18] The most common protocols were doxorubicin, cyclophosphamide, taxane and trastuzumab (ACTH; 64 patients) and docetaxel, carboplatin and trastuzumab (TCH; 35 patients). Using dispensing claims, we identified 13 unique protocols using dispensing claims, five of which were consistent with clinical guidelines. The most common protocols from dispensing data were ACTH (35 patients), TCH (32 patients) and doxorubicin, taxane and trastuzumab (A-TH; 25 patients; Table 2).

Overall, 76 protocols (69%) based on combinations of medicine therapies in prescribing data matched protocols of the same combination of medicine therapies in dispensing claims. We found that 32 of 35 (91.4%) TCH protocols were consistent across dispensing and prescribing data, but only 35 of 64 (54.7%) ACTH protocols matched across prescribing and dispensing data. This difference was driven almost entirely by the absence of cyclophosphamide in the dispensing claims of 25 patients, all of whom were general beneficiaries for

Table 1. Patient characteristics (*N* = 110)

Characteristic	Category	*n* (%)
Sex	Female	110 (100.0)
Age at diagnosis (years)	Median	53
	Range	21–86
PBS entitlement status	General beneficiary	66 (60.0)
	Concessional beneficiary	25 (22.7)
	General and concessional	19 (17.3)
Cancer stage	1	38 (34.5)
	2	47 (42.7)
	3	25 (22.7)
Tumour grade	1	2 (1.8)
	2	22 (20.0)
	3	85 (77.3)
	Not recorded	1 (0.91)
Hormone receptor profile	ER + / PR +	45 (40.9)
	ER + / PR –	21 (19.1)
	ER – / PR +	1 (0.9)
	ER – / PR –	43 (39.1)

ER = oestrogen receptor; PBS = Pharmaceutical Benefits Scheme; PR = progesterone receptor

all or part of the study period. Assuming that the patients receiving A-TH, based on dispensing claims, also received cyclophosphamide (which is below the general beneficiary copayment and thus not captured in PBS claims), then 60 of 64 (93.8%) patients receiving ACTH protocols according to prescribing data also received ACTH based on dispensing data.

Other discrepancies between prescribing and dispensing claims included three patients who were initially diagnosed with early breast cancer and therefore were eligible for inclusion in this study who were later diagnosed with metastatic disease. These patients would have had their treatment subsidised on the herceptin program, which is a separate program outside the PBS, and hence trastuzumab treatments were not captured in the PBS records. One patient received trastuzumab as a part of a clinical trial, and this is not captured in the PBS data. One patient was intended to receive ACTH and was dispensed all medicines comprising the protocol, but then switched treatment protocols.

We identified 57 patients who were prescribed hormone therapy from medical records, all of whom were dispensed hormone therapy. However, we found an additional 20 patients with evidence of dispensed hormone therapy in dispensing records. Hormone therapies were underrepresented in prescription data, regardless of the type of the therapy.

Number of treatment cycles and duration of therapy

We found the median number of medicine treatments for each protocol was underestimated in dispensing data. This difference was most marked in protocols where paclitaxel was administered, such as ACTH, where the median number of treatments was 44 in prescription data and 30 in dispensing data (Table 3).

The median duration of treatment was similar across prescription and dispensing data for patients with matched protocols. Duration of therapy for ACTH was 443 days in prescription data and 422 in dispensing data (Table 4). However, these estimates were less consistent where there were small numbers of patients receiving the protocols. In these instances, dispensing data underestimated treatment duration in three patients who received docetaxel, cyclophosphamide and trastuzumab (289 vs 377 days) and overestimated in five patients who received paclitaxel and trastuzumab (385 vs 371 days).

Table 2. Treatment protocol concordance: prescription versus dispensing claims data (*N* = 110)

Prescription data		Dispensing data			
Treatment protocol	No. patients	Treatment protocol	No. patients	Concordance (%)	Reason for discrepancy
ACTH	64	ACTH	35	54.7	–
		A-TH	25	0	No cyclophosphamide
		AC-T	2	0	No trastuzumab
		ACTH/capecitabine	1	0	Additional capecitabine
		TH	1	0	No doxorubicin or cyclophosphamide
TCH	35	TCH	32	91.4	–
		Docetaxel/trastuzumab	1	0	No carboplatin
		Carboplatin	1	0	No docetaxel and trastuzumab. Patient enrolled in trial
		AC-TCH	1	0	Initially planned for ACTH then switched to TCH. Both AC and TCH dispensed but patient only received TCH
TH	5	TH	5	100	–
Docetaxel, cyclophosphamide and trastuzumab	3	Docetaxel, cyclophosphamide and trastuzumab	3	100	–
FEC-DH	2	FEC-DH	1	50	–
		FE-DH	1	0	No cyclophosphamide
Docetaxel, doxorubicin, cyclophosphamide, followed by docetaxel and trastuzumab	1	Docetaxel, doxorubicin and cyclophosphamide	1	0	No trastuzumab
Hormone therapy: tamoxifen 20 mg[a]	22	Tamoxifen 20 mg[a]	31	71.0	Information on prescription data is only from medical notes
Hormone therapy: anastrazole 1 mg	20	Anastrazole 1 mg	24	83.3	
Hormone therapy: letrozole 2.5 mg	15	Letrozole 2.5 mg	18	83.3	
Hormone therapy: exemestane 25 mg	0	Exemestane 25 mg	1	0	
Hormone therapy: toremifene 60 mg	0	Toremifene 60 mg	1	0	
Hormone therapy: goseralin 3.6 mg	0	Goseralin 3.6 mg	2	0	

AC-T = doxorubicin, cyclophosphamide and taxane; AC-TCH = doxorubicin, cyclophosphamide, docetaxel, carboplatin and trastuzumab; ACTH = doxorubicin, cyclophosphamide, taxane and trastuzumab; A-TH = doxorubicin, taxane and trastuzumab; FEC-DH = 5-fluorouracil, epirubicin, cyclophosphamide, docetaxel and trastuzumab; FE-DH = 5-fluorouracil, epirubicin, docetaxel and trastuzumab; TCH = docetaxel, carboplatin and trastuzumab; TH = paclitaxel and trastuzumab

[a] One patient had both tamoxifen 10 mg and tamoxifen 20 mg in dispensing claims

Table 3. Median number of treatments received per protocol for patients with matched protocols in prescription data and dispensing claims (n = 109)

	Patients with complete data ascertainment and matched protocols in prescription and dispensing data (n = 76)					Patients with nonmatched protocols in prescription and dispensing data (n = 33)				
		Prescription data		Dispensing data			Prescription data		Dispensing data	
Treatment	No. patients	Median no. treatments	Range	Median no. treatments	Range	No. patients	Median no. treatments	Range	Median no. treatments	Range
ACTH	**35**	**44**	**21–46**	**30**	**12–40**	**29**	**44**	**29–60**	**26**	**5–49**
–Doxorubicin	35	4	3–4	4	3–6	29/25	4	3–4	4	3–7
–Cyclophosphamide	35	4	3–4	4	3–5	29/1	4	3–4	3	0–4
–Paclitaxel	35	12	6–13	7	3–13	28	12	7–12	6	2–12
–Docetaxel	0	4	0	0	0	1	4	0	4	0
–Trastuzumab	35	24	4–26	17	3–21	27	25	17–41	17	3–18
TCH	**32**	**29**	**19–29**	**26.5**	**13–30**	**3**	**29**	**25–29**	**21**	**6–31**
–Carboplatin	32	6	2–6	4	1–6	3/2	6	4–6	6	6–6
–Docetaxel	32	6	2–6	5.5	2–7	3/2	6	4–6	5	4–6
–Trastuzumab	32	17	11–17	17	5–18	3/2	17	17–17	17	17–17
TH	**5**	**28**	**10–32**	**19**	**16–28**	**0**	**0**	**0**	**0**	**0**
–Paclitaxel	5	8	3–12	6	2–10	0	0	0	0	0
–Trastuzumab	5	17	5–24	15	13–18	0	0	0	0	0
Docetaxel / cyclophosphamide / trastuzumab	**3**	**25**	**25–27**	**21**	**15–25**	**0**	**0**	**0**	**0**	**0**
–Cyclophosphamide	3	4	4–4	4	4–4	0	0	0	0	0
–Docetaxel	3	4	4–4	4	4–4	0	0	0	0	0
–Trastuzumab	3	17	17–19	13	7–17	0	0	0	0	0
FEC-DH	**1**	**16**	**0**	**16**	**0**	**1**	**29**	**0**	**24**	**0**
–Fluorouracil	1	3	0	3	0	1	3	0	1	0
–Epirubicin	1	3	0	3	0	1	3	0	3	0
–Cyclophosphamide	1	3	0	3	0	1	3	0	-	0
–Docetaxel	1	3	0	4	0	1	3	0	3	0
–Trastuzumab	1	4	0	3	0	1	17	0	17	0

ACTH = doxorubicin, cyclophosphamide, taxane and trastuzumab; FEC-DH = 5-fluorouracil, epirubicin, cyclophosphamide, docetaxel and trastuzumab; TCH = docetaxel, carboplatin and trastuzumab; TH = paclitaxel and trastuzumab
Note: One protocol in prescription data was outside evidence based guidelines and was excluded from further analysis, resulting in n = 109 patients.

Table 4. Durations of treatment per protocol for patients with matched protocols in prescription data and dispensing claims (n = 109)

	Patients with complete data ascertainment and matched protocols in prescription and dispensing data (n = 76)					Patients with nonmatched protocols in prescription and dispensing data (n = 33)				
		Days on treatment					Days on treatment			
		Prescription data		Dispensing data			Prescription data		Dispensing data	
Treatment	No. patients	Median	Range	Median	Range	No. patients	Median	Range	Median	Range
ACTH	**35**	**443**	**170–689**	**422**	**155–492**	**29**	**438**	**290–829**	**424**	**46–514**
–Chemotherapy	35	177	153–430	165	127–232	29	172	156–189	168	31–514
–Trastuzumab	35	366	51–689	361	91–431	29/27[a]	373	219–796	359	31–422
TCH	**32**	**367**	**93–424**	**368**	**30–429**	**3**	**373**	**364–397**	**361**	**134–372**
–Chemotherapy	32	134	51–144	126	65–170	3	134	93–135	128	80–134
–Trastuzumab	32	367	239–408	366	114–415	3/2[b]	373	364–397	366.5	361–372
TH	**5**	**371**	**65–404**	**385**	**253–434**	**0**	**0**	**0**	**0**	**0**
–Chemotherapy	5	82	49–107	64	40–116	0	0	0	0	0
–Trastuzumab	5	371	65–404	381	253–434	0	0	0	0	0
Docetaxel / cyclophosphamide / trastuzumab	**3**	**377**	**366–415**	**289**	**154–363**	**0**	**0**	**0**	**0**	**0**
–Chemotherapy	3	94	93–100	103	92–129	0	0	0	0	0
–Trastuzumab	3	377	366–415	289	154–363	0	0	0	0	0
FEC-DH	**1**	**180**	**0**	**68**	**0**	**1**	**436**	**0**	**407**	**0**
–Chemotherapy	1	137	0	68	0	1	135	0	107	0
–Trastuzumab	1	95	0	53	0	1	380	0	380	0

ACTH = doxorubicin, cyclophosphamide, taxane and trastuzumab; FEC-DH = 5-fluorouracil, epirubicin, cyclophosphamide, docetaxel and trastuzumab; TCH = docetaxel, carboplatin and trastuzumab; TH = paclitaxel and trastuzumab
[a] 29 patients in prescription data / 27 patients with trastuzumab in the dispensing data
[b] 3 patients in prescription data / 2 patients with trastuzumab in the dispensing data
Note: One protocol in prescription data was outside evidence based guidelines and was excluded from further analysis, resulting in n = 109 patients.

Discussion

This study demonstrates that PBS dispensing data can be used to reliably estimate cancer medicine use in HER2-positive early breast cancer. Protocols constructed from dispensing claims were consistent with protocols derived from prescription records in patients who had complete ascertainment of dispensing data. Further, treatment duration estimates based on dispensing claims accurately reflected estimates based on prescribing data, but dispensing claims did not accurately reflect the number of treatment cycles patients received.

We underestimated the median number of treatments in dispensing data because vials dispensed could be used for more than one cycle; therefore, some therapies were administered more frequently than they were dispensed. This was most evident in ACTH, where paclitaxel was usually given with trastuzumab on a weekly basis (prescription data), but dispensed on a 3-weekly basis.

At the time this study was undertaken, there were a number of policies relating to the administration and collection of dispensing data that have subsequently changed. First, since April 2012, all PBS-listed treatments, regardless of whether the Commonwealth pays a subsidy are captured in PBS records.[11] Second, since December 2011, the efficient funding of chemotherapy has meant that patients are dispensed vial combinations that most cost effectively comprise the required patient doses.[20] This is likely to result in more accurate measurement of dosage received.

Trastuzumab and the accompanying chemotherapy used for early breast cancer treatment are given intravenously in the hospital setting and accurately reflected in medication charts as they are signed before administration. However, oral therapies are self-administered by patients. Therefore, it is not surprising that PBS dispensing claims for oral hormone therapies appeared to better ascertain this information than the medical charts. Therefore, our study has demonstrated that dispensing data is likely to reflect prescription data for intravenous cancer treatments but dispensing claims better reflect exposure to oral therapies.

Our study was conducted in one Australian area health service. We had an excellent response rate of 74%, meaning this cohort of patients is likely to reflect most patients receiving treatment in the study period. Although the treatment practices reported in this study may not necessarily reflect those across oncology practice in Australia, it is likely that our study findings are applicable nationally, but may not be generalisable to other therapies or jurisdictions.

Conclusions

Recent changes to the way cancer treatments are subsidised in Australia and the complete capture of PBS dispensings will lead to more accurate measurement of cancer treatment in claims data. Our findings provide a foundation for future population-level research examining the use and outcomes of cancer therapies in routine care.

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Competing interests

None declared

Author contributions

CH was responsible for the study design, protocol development, collection of data, oncology input and preparation of the manuscript. BD was responsible for the statistical analysis and preparation of the manuscript. RW was responsible for the study design, oncology input and preparation of the manuscript. S-AP was responsible for the study design, protocol development, pharmacoepidemiology expertise and preparation of the manuscript.

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