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ORIGINAL REPORT

Trastuzumab and Metastatic Breast Cancer: Trastuzumab Use in Australia—Monitoring the Effect of an Expensive Medicine Access Program

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ABSTRACT

Purpose
Data from clinical trials are used for drug registration; however, many cancer medicines are ultimately used off-label. This study examines the extent to which the clinical practice use of trastuzumab for the treatment of metastatic breast cancer differs from its use under trial conditions.

Methods
This study involved all women (N = 1,469) with metastatic breast cancer who received trastuzumab in Australia between December 2001 and March 2005. Given that Australia operates a universal health care system, administrative databases could be examined to determine the duration of therapy, rate of off-label use, compliance with cardiac monitoring, and the extent of drug wastage (volume and cost).

Results
A total of 433 enrollees (29.5%) received trastuzumab as monotherapy and 1,036 enrollees (70.5%) received the drug in combination with chemotherapy. A total of 321 women (22%) received off-label trastuzumab. The median duration of trastuzumab therapy was longer than that on trial: 5.6 *v* 3.1 months for enrollees receiving monotherapy and 12.5 *v* 6.9 months for concomitant chemotherapy. Only 47 (3%) of enrollees received cardiac monitoring before and during trastuzumab therapy. We estimated 24% of trastuzumab dispensed was discarded, at a cost of $21.1 million Australian. Alternative administration schedules and the addition of another vial size potentially reduce wastage to 6% of volume dispensed.

Conclusion
Debates about the use of expensive cancer medicines should consider postmarketing assessments as well as trial experience. The longer duration of trastuzumab use in clinical practice and the high rates of off-label use provide incentive for new clinical trials. Strategies to improve cardiac monitoring and to minimize drug wastage are issues that require immediate attention.

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INTRODUCTION

Much of what we know about the benefits and toxicities of drug treatments are based on phase III clinical trials, conducted in highly select populations receiving exceptionally good care. The pressure to subsidize drugs that potentially improve the length of life and/or quality of life is intense. Consequently, more drugs are approved for marketing on the basis of interim data, before benefits and risks have been quantified fully.[1] Data derived from the real-world setting may be the only opportunity to study the benefits and risks associated with new drugs and estimate the extent of off-label use in large numbers of typical patients. However, postmarketing observational studies are not routine in most countries. In a recent debate about the increasing costs of cancer care, experts called for the evidence base for new treatments to be improved for the purpose of improving patient management and informing resource allocation decisions.[2-4]

Increasing health care costs must be considered from the perspective of the payer. In the United States, individuals or private health providers frequently subsidize drug costs. In contrast, Australia, like most of Europe, operates a universal health system involving public and private sectors. Under single user–pay systems, individual wealth or health insurance status does not influence access to taxpayer-funded drugs or medical services. Not unexpectedly, cost-effectiveness analysis is used frequently to assist government payers to make decisions about whether a new therapy should be made available to the population. Given that the

Australian government bears the cost of health care, it has comprehensive data, based on payment, for the services and drugs provided to its citizens.

The recombinant antibody trastuzumab (Herceptin, Genentech, South San Francisco, CA) exemplifies the new generation of targeted anticancer therapies. Trastuzumab inhibits the growth of breast cancer cells by binding to human epidermal growth factor receptor 2 (HER-2). Overexpression of this receptor is found in approximately 25% of breast cancers and occurs as a consequence of amplification of the *HER2/neu* gene.[5,6] Clinical trials demonstrated trastuzumab, used alone[7] or in combination with chemotherapy,[8] slowed the progression of HER-2–positive metastatic breast cancer. In patients failing prior chemotherapy for metastatic breast cancer, trastuzumab used as a single agent reduced tumor size in 15% of patients.[7] In individuals not receiving prior chemotherapy, the combination of cytotoxics and trastuzumab delayed time to metastatic disease progression by about 3 months.[8] More recently, studies have shown that trastuzumab prevents disease recurrence, at least in the short term, in women with early-stage breast cancer.[9-12] In comparison with chemotherapy, trastuzumab is well tolerated and has few acute adverse effects. However, retrospective analysis of trial data and single institutional case reviews[13,14] have shown trastuzumab causes cardiac failure, particularly when administered concurrently with anthracyclines.[15] In contrast to metastatic breast cancer studies, trastuzumab trials in early breast cancer have excluded individuals with preexisting heart disease and incorporated compulsory cardiac monitoring in their design.[9-12]

Despite the clinical efficacy of trastuzumab, the price of this drug places it beyond the reach of most individuals (approximately $55,000 Australian dollars [AUD] for a 70-kg patient for 1 year of treatment). Not surprisingly, regulatory approval of trastuzumab was closely followed by campaigns lobbying for public subsidy. In Australia, trastuzumab was not considered cost effective for the treatment of metastatic breast cancer, and was not approved for listing on the Pharmaceutical Benefits Schedule, Australia's list of government-subsidized medicines. Under intense pressure, the federal government took the unprecedented decision of creating a taxpayer-funded Herceptin Program entirely outside the Pharmaceutical Benefits Scheme (PBS). Since December 2001, the Herceptin Program has provided free trastuzumab access to treat HER-2–positive metastatic breast cancer. To emulate trastuzumab use in the pivotal clinical trials[7,8] and to ensure drug use complied with registered indications, a number of restrictions to trastuzumab access were imposed by Medicare Australia, the Herceptin Program administering body (Table 1).[16]

In this study, we use Australian national health administrative databases to examine trastuzumab use for the treatment of metastatic breast cancer. Specifically, we determine the duration of trastuzumab therapy, extent of off-label use, extent to which patients undergo cardiac monitoring, and wastage (volume and cost) associated with trastuzumab administration schedules and the discarding of unused vial portions. Finally, these findings are compared with the usage patterns reported in the key clinical trials.

METHODS

Data Sources and Extraction

This study was approved by the St Vincent's and Mater Health, Sydney Human Research Ethics Committee, and the Medicare Australia External Request Evaluation Committee. Three Medicare Australia databases (Table 2) were supplied to evaluate the Herceptin Program between December 2001 and March 2005. To protect patient confidentiality, Medicare Australia staff extracted data from the program database and allocated a unique scrambled identifier to the records of each enrollee. These same identifiers were then assigned to enrollees' PBS and Medicare Benefits Scheme (MBS) records. All three databases were supplied to the investigators, stripped of name and address identifiers, and subsequently linked to enable person-level data analysis. SAS software, version 8 (SAS Institute Inc, Cary, NC) was used for statistical analyses.

Duration of Trastuzumab Therapy

Duration of trastuzumab therapy was calculated as the period from the first trastuzumab dispensing date to the last dispensing date plus an additional 30 days (it is standard practice under the program to dispense trastuzumab as a 1-month supply). A period of more than 90 days between trastuzumab dispensing records was considered a separate period of exposure. Program and PBS dispensing records were used to classify enrollees according to whether their first period of trastuzumab exposure (hereafter referred to as the first course of therapy) was administered as monotherapy or as concomitant chemotherapy. Enrollees were included in the concomitant chemotherapy group if they were identified in the program database as receiving trastuzumab with taxanes, or were identified in the program database as receiving monotherapy but had evidence of at least two PBS chemotherapy dispensing records (Appendix Table A1, online only) more than 7 days apart during their first course of trastuzumab therapy. All remaining enrollees were included in the monotherapy group. Off-label trastuzumab use was determined by identifying cohort members administered trastuzumab outside its registered indications for use (Table 1). For example, patients with off-label use were those registered in the program as receiving trastuzumab as monotherapy with at least two PBS dispensing records for taxane or nontaxane chemotherapy, or those registered to receive trastuzumab with taxanes who had at least two PBS dispensing records for second-line nontaxane chemotherapy.

Table 1. Eligibility for Herceptin in Australia[16]

Under the Herceptin Program, trastuzumab is available free to Australian patients
With HER-2–positive metastatic breast cancer either in combination with taxanes for patients who have not received chemotherapy for metastatic disease
As monotherapy for the treatment of those patients who have received one or more chemotherapy regimen(s) for metastatic disease
Patients must
Have IHC evidence of HER-2 protein at the 3+ level, or
Have IHC evidence of HER-2 protein at the 2+ level, subsequently confirmed as exhibiting *HER2* gene amplification by FISH, or
Exhibit *HER2* amplification by FISH

NOTE. Prescribers must register the patient with Medicare Australia for participation in the Herceptin Program and confirm patient registration every 6 months. To register, the prescriber must provide evidence that the patient is eligible (via faxed pathology reports and verbal confirmation), evidence of patient and prescriber consent, and patient details including patient weight (as dosage is based on weight).
Abbreviations: HER-2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.

Table 2. Characteristics of the Medicare Australia Data Sources

Database	Description	Period	Data Extracted	Data Capture
Herceptin Program	Program participants	December 2001-March 2005	Year of birth, state of residence, postal code, patient weight at program commencement, treatment qualification*, type of therapy†, trastuzumab-dispensing dates	All individuals qualifying for trastuzumab therapy on the Herceptin Program
PBS	Medicines dispensed	January 2001-March 2005	PBS pharmaceutical item code, drug name, strength, anatomical therapeutic chemical classification, date of supply, number of prescriptions supplied and repeats	Data recorded from prescriptions for which the pharmaceutical item cost is greater than the patient contribution (at the general or concessional rate); medicines dispensed to public hospital inpatients are not captured
MBS	Medical services billed	January 2001-March 2005	Date of service and MBS item code	Services that qualify for Medicare benefits, such as doctor visits, pathology, and diagnostic testing; only claims information is collected so diagnostic and clinical information is not available; services provided to public hospital inpatients and public hospital emergency departments are not captured

Abbreviations: PBS, Pharmaceutical Benefits Scheme; MBS, Medicare Benefits Scheme; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.
*IHC 3+, IHC 2+, and confirmed by FISH, or FISH only.
†Trastuzumab as monotherapy or trastuzumab with taxanes.

The median duration of trastuzumab therapy (excluding gaps in therapy of more than 90 days) was estimated for enrollees with a minimum program follow-up period equivalent to the pivotal trials (15 months for monotherapy[7] and 31 months for concomitant chemotherapy[8]). Kaplan-Meier survival methodology also was used to estimate the duration of the first course of trastuzumab therapy based on data from the entire program cohort, irrespective of follow-up time.

Cardiac Monitoring

The number of echocardiography (MBS item code 55113 corresponding to International Classification of Diseases, 10th revision, code 55112) and/or multiple gated acquisition (MUGA) scans (MBS and International Classification of Diseases, 10th revision, code 61313) occurring 30 days before the first course of trastuzumab therapy and at any time during the first course of therapy was determined. The relationship between cardiac monitoring and anthracycline use (defined as one or more PBS anthracycline dispensing records preceding or occurring at any time during the first course of trastuzumab therapy) was also assessed.

MBS items are for tests subsidized by the federal government. Program enrollees may also have had echocardiography and MUGA scans performed as inpatients in state-funded hospitals (these procedures are not captured in the MBS data). In the absence of unit record data on program enrollees from state-based data sources, aggregated data from the MBS online statistics[17] and National Hospital Morbidity Data procedures database[18] were used to estimate the extent to which echocardiography and MUGA scans are captured in hospital data collections compared with MBS data. For the purposes of the analysis the National Hospital Morbidity Data, data were restricted to separations for tests performed on day-only admissions, given that the majority of oncology patients are in this category. Between July 2000 and June 2006, 99% of MUGA scans and echocardiograms recorded in the two databases were captured in the MBS database.

Trastuzumab Wastage

Trastuzumab is packaged in one 150-mL vial (concentration, 1 mg/mL) and dosing is calculated according to patient weight. In Australia, it is mandated that when only a portion of a vial is required for a patient, the unused balance must be discarded.[19] Program enrollees received trastuzumab as a 4 mg/kg loading dose and 2 mg/kg standard weekly dose. The volume of trastuzumab dispensed (in liters) and discarded during the study period, and associated expenditure based on a vial cost of AUD$1,031.21[20], was calculated. Volume calculations assumed one dispensing record equated to 1 month of therapy, a 90-day break in therapy was a separate course of therapy (requiring a loading dose at the beginning of the next course), and patient weight remained constant throughout the treatment period. Sensitivity analyses were conducted to assess the impact of a 3-week dosing schedule (8 mg/kg loading dose and 6 mg/kg standard dose once every 3 weeks) and of the availability of additional vial sizes (150 plus 100 mL or 150 plus 200 mL).

RESULTS

Between December 2001 and March 2005, 1,469 women with HER-2–positive metastatic breast cancer were enrolled onto the Herceptin Program. The average age of the cohort was 54.3 years (range, 22 to 95 years); 7% (n = 103) of enrollees were between 75 to 84 years old and 1.3% (n = 19) were age ≥ 85 years. The average weight of the cohort was 69.9 kg (range, 29 to 150 kg) and 74% of women were 50 to 75 kg. Eighty-eight percent (n = 1,291) of enrollees had HER-2–positive breast cancer as demonstrated by 3+ immunohistochemistry, 3.8% (n = 56) demonstrated by fluorescent in situ hybridization (FISH) gene amplification, and 8.3% (n = 122) demonstrated by 2+ immunohistochemistry and confirmatory FISH testing.

Herceptin Program records indicated 662 enrollees (45.1%) received trastuzumab as monotherapy and 807 enrollees (54.9%) received the drug in combination with taxanes. On the basis of program and PBS records, 1,036 (70.5%) enrollees received concomitant

chemotherapy at some time during their first course of trastuzumab therapy. Of these individuals, 761 received taxanes alone, 192 received taxanes and nontaxane chemotherapy, and 83 were treated with nontaxane chemotherapy alone. Of program enrollees receiving other chemotherapy, 213 received vinorelbine and 33 received anthracyclines (Table 3); 321 women (22%) received off-label trastuzumab (Table 4).

Duration of Therapy

For program enrollees who had a minimum follow-up period equivalent to that of the pivotal clinical trials, the median duration of trastuzumab therapy was 4.9 months (range, 1.0 to 40.2 months) for monotherapy, and 11.6 months (range, 1.0 to 41.3 months) for enrollees receiving trastuzumab with chemotherapy (Table 5). A total of 96 enrollees had a break in treatment of more than 90 days and at least one additional period of exposure to trastuzumab therapy. When the additional exposure periods were incorporated in the estimates, duration of therapy increased to 5.9 months (range, 1.0 to 40.2 months) for monotherapy, and 12.7 months (range, 1.0 to 41.3 months) for enrollees receiving trastuzumab with chemotherapy. For the entire program cohort, the estimated median duration of the first course of trastuzumab therapy (based on Kaplan-Meier methodology) was 5.6 months (range, 1.0 to 40.2 months) for enrollees receiving trastuzumab as monotherapy and 12.5 months (range, 1.0 to 41.3 months) for enrollees receiving trastuzumab with concomitant chemotherapy (Table 5). Thus, the duration of therapy in clinical practice was longer than that observed in the pivotal trials (Table 5).

Cardiac Monitoring

A total of 158 (10.8%) women received cardiac monitoring up to 30 days before the commencement of the first course of trastuzumab therapy, 378 women (25.7%) were monitored at some time during the first course of therapy, and 47 women (3.2%) were monitored before and during their first course of therapy. Anthracycline use, before or during trastuzumab therapy, did not influence the frequency of cardiac monitoring.

Trastuzumab Wastage

During the 40-month period, an estimated 87,102 trastuzumab vials were dispensed (costing AUD$88.9 million) and 3,100 L or the equivalent of 20,667 vials of unused trastuzumab were discarded (costing AUD$21.1 million). Thus, 24% of all trastuzumab dispensed during the period was discarded. On the basis of dosing once every 3 weeks rather than a weekly dosing schedule, 13% of total volume would have been discarded (11,014 L dispensed; 1,383 L discarded), accompanied by an AUD$18.3 million reduction in cost. On the basis of dosing once every 3 weeks and the availability of the existing 150-mL vial and a 100- or 200-mL vial, wastage would have been reduced to 5% of total volume dispensed (9,669 L dispensed and 508 L discarded).

Table 3. Number of Herceptin Program Enrollees Receiving Chemotherapy During Their First Course of Trastuzumab With and Without Taxanes

Chemotherapy	Taxanes With Other Chemotherapy* (n = 192)	Other Chemotherapy Without Taxanes (n = 83)
Anthracyclines	23	10
Platinum compounds	44	12
Thiotepa	0	0
Methotrexate	3	2
Vinblastine	0	0
Vinorelbine	146	67
Etoposide	0	1

*Other chemotherapy was administered at some stage during trastuzumab therapy, but not necessarily at the same time as the taxanes.

Table 4. Trastuzumab Use According to Herceptin Program Records (registered indication) and Actual Use (validation with PBS records)

Therapy	Herceptin Program Records: Monotherapy (n = 662)	Herceptin Program Records: With Taxanes (n = 807)
Monotherapy	433	Nil
With taxanes alone	94*	667
With taxanes and nontaxane chemotherapy	52*	140 (92)*
With nontaxane chemotherapy alone	83*	Nil

Abbreviation: PBS, Pharmaceutical Benefits Scheme.
*Off-label use.

DISCUSSION

In this study, health administrative databases were used to examine, for the first time to our knowledge, trastuzumab use for the treatment of metastatic breast cancer outside trial conditions. We highlight the way that real-word clinical practice deviates from trial conditions and the limitations of using clinical trial outcomes as the sole source of evidence to inform resource allocation decisions. The cost effectiveness of trastuzumab in the treatment of metastatic breast cancer is determined, in part, by the duration and cost of therapy per patient. Our study suggests the duration of trastuzumab treatment in clinical practice is longer than that observed under trial conditions (Table 5). In drawing this conclusion, we relied on the fact that time to progression, as reported in the pivotal clinical trials, was a close estimate for treatment duration (Roche Products Pty Ltd, New South Wales, Australia, personal communication, January 2007). The longer duration of therapy in clinical practice may reflect a greater benefit of trastuzumab, perhaps because of better HER-2 target identification (Table 5), or the concomitant use of more effective (albeit off-label) nontaxane chemotherapies.[21] An alternative explanation may be that the longer treatment durations simply reflect a reluctance on the part of physicians and patients to cease a drug viewed as doing no harm.[22] According to this viewpoint, disease progression while patients are receiving trastuzumab therapy may be addressed by changing the chemotherapy regimen without ceasing trastuzumab. This proposition is supported by our finding that a significant number of enrollees received additional or alternative chemotherapy treatments (mainly vinorelbine) at some stage during trastuzumab therapy. This occurred even though trastuzumab is only registered for use with taxanes. Although extended therapy and the addition of new chemotherapy partners may be beneficial, this treatment strategy should be evaluated in well-designed clinical trials.

Our study also illustrates the potential financial savings associated with more appropriate diagnostic tests for HER-2 status or alternative vial sizes. Selection for trastuzumab therapy relies on the accurate determination of HER-2 status, which is currently best

Table 5. Herceptin Program Versus the Pivotal Phase II and III Trastuzumab Trials

Characteristic	Herceptin Program		Clinical Trials		
				Phase III Trastuzumab + Chemotherapy* Arms[8]	
	Single-Agent Trastuzumab	Trastuzumab + Chemotherapy*	Phase II Single-Agent Trastuzumab[7]	Trastuzumab + AC	Trastuzumab + Paclitaxel
No. of patients	433	1,036	222	143	92
Age, years					
Mean	56	53	54	54	51
Range	22-95	26-92	28-86	27-76	25-77
HER-2 assessment					
2+ on IHC			50	35	24
3+ on IHC	377	914	172	108	68
FISH	56	122			
Duration of therapy, months					
First course, minimum follow-up period equivalent to trials					
Median	4.9†	11.6‡			
Range	1.0-40.2	1.0-41.3			
Kaplan-Meier analysis					
Median	5.6	12.5			
Range	1.0-40.2	1.0-41.3			
Inferred from time to progression					
Median			3.1§	7.8§‖	6.9§‖
Range			0.0-28.0		

Abbreviations: HER-2, human epidermal growth factor receptor 2; AC, anthracycline and cyclophosphamide; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.
*Concomitant chemotherapy.
†n = 273.
‡ = 291.
§Time to progression observed in the studies is a reasonable and close estimate to the treatment duration (Roche Products Pty Ltd, New South Wales, Australia, personal communication, December 2006).
‖Range not reported in article.

performed using assays detecting *HER2* gene amplification (for example by FISH).[23] In contrast, 70% to 80% of breast cancers assessed as 2+ by immunohistochemistry and 16% to 30% of cancers assessed as 3+ by this technique do not have *HER2* amplification.[24-26] Nearly 90% of women accessing the Herceptin Program had 3+ tumor immunostaining, and Australian data suggest 20% of these are false-positive results.[24] Therefore, it is likely that up to 270 program enrollees did not gain a benefit from trastuzumab therapy because their tumor was not HER-2 positive. Conversely, some patients, inevitably, did not qualify for Herceptin Program treatment because of false-negative immunostaining results.[26] The inaccurate identification of the HER-2 target, whether in a trial setting or clinical practice, may result in inappropriate and wasteful use of this expensive therapy.

Additional sources of trastuzumab wastage relate to its supply in a single vial size and weekly administration schedules. During the first 40 months of the Herceptin Program, nearly one fourth of trastuzumab dispensed was discarded, at an estimated cost of AUD$21.1 million. Nearly 4 years after the program started, dosing schedules once every 3 weeks were approved—a change that potentially reduces wastage by half. Repackaging to provide an additional vial size could reduce wastage further to less than 6% of total volume dispensed and thus improve the cost effectiveness of trastuzumab. Although some drug wastage is inevitable, it is also clear that altering vial sizes and administration schedules are simple cost-containment measures that can be implemented without adversely affecting patient outcomes.

An alarming study finding was the low rate of cardiac monitoring. Only 3% of enrollees underwent echocardiography or MUGA scans before or during trastuzumab therapy. Women with previous or concomitant anthracycline therapy were no more likely to receive cardiac monitoring than were women in other groups. A most disturbing finding was that 33 program enrollees received at least two cycles of concomitant anthracyclines despite compelling evidence that this places them at significant risk for cardiotoxicity.[8,13,15] Trastuzumab currently is available for the treatment of early-stage breast cancer and the pressure to use this drug is intense.[27] Given our findings on the extent of cardiac monitoring in the metastatic setting, it is conceivable and of concern that women with early-stage breast cancer may also fail to receive adequate monitoring.

Our study has several limitations. The data sources used were established for the reimbursement of items billed under three federally funded community programs and contain no clinical data. However, secondary health data sources have been used routinely and are considered a valid and reliable means of evaluating the impact of pharmaceutical interventions.[28] This study was limited further by the inability to link the national data sources to state and territory collections such as hospitals admissions, procedures performed on hospital inpatients, and the death register. For this reason, our analysis may have underestimated the use of investigative procedures. However, given that most Australian oncology practice occurs in the community setting, the magnitude of these underestimations is likely to be small.

There is little doubt that many Australians with metastatic HER-2–positive breast cancer benefited from trastuzumab treatment; however, it is clear that this expensive drug has not always been prescribed appropriately. Enormous pressure is placed on regulatory bodies

worldwide to use fast-track drug approval before the full extent of benefits and risks are evaluated. Given these pressures, and those placed on public and private health insurers to make the drugs affordable to individuals, it is imperative that outcomes of observational studies complement trial evidence, inform the design of additional clinical trials, and inform clinical practice and policy decision making.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).