

## RESEARCH ARTICLES

# Pharmacists' Role in Targeted Cancer Therapy in Australia and Implications for Pharmacy Education

David M. Plevin, BPharm,<sup>a</sup> Helena M. Ward, PhD,<sup>b</sup> Michael B. Ward, PhD,<sup>a</sup> Michael J Sorich, PhD,<sup>a</sup> and Ross A. McKinnon, PhD<sup>a</sup>

<sup>a</sup>University of South Australia, Adelaide

<sup>b</sup>Flinders University, Bedford Park, Australia

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**Objectives.** To investigate the pharmacists' role in providing targeted therapies to patients and its implications for pharmacy education.

**Methods.** Nine pharmacy faculty members, 12 clinical pharmacists, and 4 oncologists from across Australia and New Zealand participated in semistructured interviews, which were analysed using the framework method.

**Results.** Education about targeted therapies was seen as being important, although content about pharmacodiagnostic tests was taught inconsistently among 7 universities. Issues including funding, clinical and diagnostic validity of tests, and time taken for turnaround of tests were perceived as impediments to the acceptance by clinicians of the utility of pharmacodiagnostic tests.

**Conclusions.** Pharmacists may be the ideal professionals to interpret test results and provide counselling for patients to assist them in compliance with targeted cancer therapies. Pharmacy education in cancer therapies is critical to training pharmacists who can assist patients in the correct use of these therapies.

**Keywords:** cancer, targeted therapy, monoclonal antibody, genomic medicine, pharmacodiagnosics

## INTRODUCTION

Since 1997, *targeted therapies* have been used as weapons in the arsenal against cancer. Targeted therapies attack specific molecules involved in the disease process of cancer, unlike the traditional cytotoxic approach of nonspecifically attacking rapidly dividing cells. Targeted therapies include monoclonal antibodies such as trastuzumab and small-molecule tyrosine kinase inhibitors such as imatinib.

Targeted cancer therapies are typically expensive. For example, imatinib costs more than US\$40,000 annually per patient. Gefitinib and trastuzumab both cost more than US\$45,000 annually per patient.<sup>1</sup> Thus, it is imperative from a pharmacoeconomic sustainability perspective and to optimize therapy for individual patients that targeted therapies are given only to those patients most likely to benefit from them. As targeted therapies are aimed at a specific molecule or molecules implicated in cancer pathogenesis, these therapies may consequently only be beneficial in subsets of the population whose cancers possess aberrations involving these targets or molecules downstream of their signaling pathways. For example,

trastuzumab is a monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is associated with a poor prognosis for breast cancer and an increased likelihood of response to trastuzumab. A patient beginning trastuzumab therapy therefore will require a diagnostic test to determine whether there is HER2 overexpression or amplification of the HER2 gene.<sup>2</sup>

Diagnostic tests play a critical role in determining the presence of molecular targets for cancer, and hence, which patients will benefit from a targeted therapy. In the United States, drug costs are often subsidized by individuals or private payers.<sup>3</sup> Private insurers typically pay for pharmacogenomic tests in cases where these tests are required or strongly recommended by drug labels approved by the Food and Drug Administration (FDA),<sup>4</sup> such as detecting HER2 overexpression with trastuzumab.<sup>5</sup> In Australia, where the Federal Government's Pharmaceutical Benefits Scheme (PBS) provides drugs to consumers at subsidized prices, diagnostic tests may be required to access subsidy for targeted agents. However, appropriate use of diagnostic tests is critical, with steps taken to ensure that tests have appropriate sensitivity and specificity to minimize the number of false positives and false negatives and their attendant health consequences. With trastuzumab, detecting HER2 gene amplification provides the best

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**Corresponding Author:** Helena Ward, Department of Medical Education, Flinders University, Bedford Park, Australia, E-mail: Helena.ward@flinders.edu.au

assessment of HER2 status. However, immunohistochemistry (a method of assigning HER2 status not necessarily correlated with gene amplification) was used to assess HER2 status before prescribing trastuzumab for 90% of women between December 2001 and March 2005 in Australia. Consequently, many patients received false positive results with immunohistochemistry tests. Up to 270 women receiving trastuzumab under the Herceptin program during this period may have received ineffective and potentially toxic therapy because they did not have HER2-positive tumors.<sup>3</sup> One American study reported that only 37% of tumors classified as HER2 2+ by immunohistochemistry had apparent HER2 gene amplification.<sup>6</sup> Furthermore, the “companion diagnostics” for targeted therapies are not always developed at the same time as the targeted therapy itself. For instance, in the case of gefitinib, used for lung cancer, retrospective studies showed that epidermal growth factor receptor (EGFR) activating mutations correlate with response to this agent.<sup>7</sup> Therefore, it is important to minimize any lag between biological observations of cancer and development and the uptake by clinicians of tests that can exploit these findings to ensure optimal outcomes for cancer patients. This paper will subsequently refer to diagnostic tests used to select therapy for patients as *pharmacodiagnostic* tests and the field as *pharmacodiagnosics*, following the terms used by authors such as Jørgensen, Nielsen, and Ejlersten.<sup>2</sup>

Observations that current cancer therapy is not based upon best use of molecular target identification techniques and that there is a delay in translating laboratory knowledge into clinical practice suggest that medicine could benefit from professionals with an intimate understanding of pharmacodiagnosics. Clearly, the utility of diagnostic tests will depend upon the knowledge base of healthcare professionals, including medical oncologists and pharmacists, who can determine which tests are appropriate for a given agent and interpret the test results. Consequently, it is important that pharmacy education reflects the role that pharmacists would have with these new therapeutic modalities. A search of the relevant literature has not found any articles regarding pharmacy education on targeted therapies. An Australian paper discusses the education of medical oncologists and recommends that medical oncologists receive training in such fields as tumor pathology and cancer genetics to increase their understanding of the cancer pathology, the limitations of cancer diagnostics, and the pharmacoeconomic benefits of providing therapy.

Based on published observations,<sup>3,8</sup> we hypothesized that healthcare professionals are insufficiently educated about targeted cancer therapies. This study examined coverage of targeted therapies within current oncology phar-

macy education and practice, and ways in which pharmacy education can be advanced to improve the outcomes of targeted therapies.

## METHODS

Face-to-face or telephone interviews were conducted with 9 academic and 12 clinical pharmacists across Australia and New Zealand. The academic staff members were from 7 different institutions, all but 1 of which had a dedicated pharmacy school. Eight of the 9 academics also had pharmacy degrees. The courses covering oncology content taught by these academics included 6 undergraduate courses and 3 master's courses (1 postgraduate and 2 graduate entry programs, where students require another degree for acceptance into the program). The 6 undergraduate courses were spread across 5 universities. The number of clinical pharmacists sought is generally consistent with the numbers needed in framework analyses to achieve the point of saturation, the point at which no new themes emerge from further interviews. The sample size of pharmacy academics was limited by the number of pharmacy schools in Australia and New Zealand. Ethics approval for conducting the interviews was granted by the Divisional Human Research Ethics Committee of the Division of Health Sciences, University of South Australia.

Semistructured interviews were conducted with the clinical pharmacists. With pharmacy academics, some of the interviews were of a semistructured nature, while the remainder included simple “fact finding” questions. Interview responses were handwritten by the interviewer. Four oncologists from South Australia also were interviewed using a similar semistructured interview format. As the number of oncologist was well below the point of saturation, the interviews with clinicians should be considered exploratory in nature.

The framework method of qualitative analysis was used in this study.<sup>9</sup> While there are a number of different qualitative analysis approaches that may be used, the framework analysis approach has been used by Haddy et al<sup>10</sup> in a previous, similar study. To reduce the subjectivity inherent in the approach of indexing and coding the data, another investigator coded the data independently. In some cases, data were coded more than once depending on whether the data fit more than 1 theme in the framework.

## RESULTS

### General Issues

**Toxicities of Targeted Therapies.** The idea that targeted therapies are toxic was a strong consensus that arose among clinical pharmacists (8/12).

**High Cost and Equity of Access.** The high cost of targeted therapies, or equity of access, was a theme raised by 10 interviewees (3/9 academics, 7/12 clinical pharmacists). One pharmacist expressed concern about public funding for potentially effective drugs in smaller patient groups such as head and neck cancer. One clinician felt that the cost factor imposed greater scrutiny of the risks and benefits of individuals being treated with a particular agent.

**Burden of Care.** Three clinical pharmacists discussed the role of the patient in administering targeted therapies. Specific issues mentioned included stressing the importance of compliance, patients taking responsibility for procuring their medicine, the patient taking the role of the supervisor/manager of administration.

**Role for All Pharmacists?** Five clinical pharmacists saw targeted therapies as something with which most pharmacists would never deal (according to 1 interviewee) or something that required handling by only appropriately trained pharmacists, at least initially. Two clinical pharmacists indicated that handling targeted therapies was a role for all pharmacists.

### Diagnostic Tests

**Funding.** Seven interviewees mentioned funding or economic implications of tests, with 1 stating that if they are within cost limitations “everyone should try to adopt them.”

One interviewee noted that these diagnostic tests could help patients save money, as well as prevent them from experiencing side effects, and that drug companies could fund testing.

**Clinician use.** Some clinicians also noted the clinical and diagnostic evidence behind tests as an issue that impeded the uptake of some pharmacodiagnostic tests. One clinician noted that surrogate markers could be used to determine whether a patient was responding to a drug, eg, the use of diastolic blood pressure as a surrogate marker for bevacizumab activity. Two interviewees noted that for tests to be useful, rapid results are needed.

**Pharmacist Roles with Diagnostic Tests.** One pharmacist believed that pharmacists’ role was to raise awareness of the availability of tests, while another believed that pharmacists could assist with interpretation of tests – both tests used for patient selection (eg, *HER2* with trastuzumab) and those used to determine whether a patient is a fast or slow metabolizer (eg, CYP450 status).

Among clinicians, 1 interviewee mentioned a role for pharmacists in biomarker assessment, both in the sense of investigating biomarkers in clinical trials and in the sense of interpreting tests. Another clinician was open to the idea of pharmacists interpreting tests; however, this person did

not believe that pharmacists were the only profession that could fill this role.

### Pharmacy Education on Targeted Therapies

**Importance of Education.** One academic and 4 clinical pharmacists noted the importance of education provision on targeted therapies. Two other clinical pharmacists believed that the onus was on the pharmacist to maintain knowledge about these agents. Two clinical pharmacists saw pharmacists’ access to oncology educational resources or relevant professionals as an important issue. The availability of targeted therapies in community pharmacies was linked by 4 clinical pharmacists to the necessity or importance of including these therapies in undergraduate education, with 1 commenting that the continuing education of community pharmacists also would need to be addressed.

**Quantity of Material Taught.** Several interviewees (2/9 academics, 3/12 clinical pharmacists) were in agreement that these agents should be taught, but that only a limited amount of material should be discussed.

**Curriculum.** Only 1 academic discussed diagnostics in any detail, stating that targeted therapies were discussed in 2 undergraduate courses and 1 master’s level course. Among the diagnostic content taught, 1 course (second year, undergraduate) discussed diagnostics in the context of the results rather than the methodology or development of the diagnostic. Another course (third year, undergraduate) covered, for trastuzumab, methods of assessing *HER2* status and the implications of false positives/negatives for these tests, and the PBS requirements for activating *EGFR* mutations with gefitinib.

The interviewee who taught the master’s level course indicated that “not a lot of detail” was presented regarding diagnostics, but a number of issues were mentioned regardless, including acquiring a tissue sample; the methods of getting positive fluorescent in situ hybridization (FISH) and immunohistochemical (IHC) tests; the frequency of positive tests; and the pros, cons and reasons for selecting different tests. An interviewee (undergraduate) from another institution mentioned that while they touched on this area, a lot of teaching was done in a subject taught earlier in that pharmacy program, including background information in genomics.

One academic who taught undergraduate courses mentioned that they previously gave a lecture on diagnostics, which subsequently had been discontinued. Other respondents indicated that little to no material was covered or that diagnostics was not discussed except in relation to PBS restrictions around subsidy of certain medications.

**Teaching Methods.** Lectures were the teaching method used in all 9 courses. One academic stated that they used cases within the lectures. Tutorials were used by 4

courses and 2 of these were case-based (although 1 case-based oncology tutorial was not necessarily about targeted therapy). Other means by which material was presented included examination content (1 course), reading associated with lecture material (1 course), and a workshop (1 course).

Two alternative education models were being used – wiki cases and self-directed learning. Self-directed learning, used by 1 course, involved students finding a recently published paper on new therapies and presenting it to their classmates. Another course posted patient cases and problem-based learning activities on a wiki platform, where students could collaborate in groups of 3 or 4 and edit one another's work. The groups identified problems, and constructed an assessment of the case and treatment plan for the patient. After presentation and grading of the cases, the wikis were made available to all students.

## DISCUSSION

Prior to conducting the interviews, diagnostics was identified as 1 of the key issues around targeted therapies. We hypothesized that lack of appropriate knowledge about pharmacodiagnostic tests among health care professionals was a barrier to their clinical implementation. This hypothesis was not directly supported by any of the interviewees, although many interviewees talked about the importance of educating pharmacists and keeping them up to date about targeted therapies and pharmacodiagnostic tests. However, this was not believed to impede the uptake of these tests.

Three general ideas that emerged from the interviews regarding pharmacy education around targeted therapies were:

- (1) Education around targeted therapies is important, especially given the recent availability of targeted therapies in community pharmacy
- (2) Only a limited quantity of material on this topic should be covered, at least at undergraduate level
- (3) Only appropriately trained pharmacists, rather than pharmacists in general, should handle targeted therapies

The finding by Corkindale, Ward, and McKinnon,<sup>11</sup> that an experienced person or system is required such that pharmacodiagnostic tests can be interpreted rapidly, indicates that pharmacists could potentially fill this gap in the health care system in a similar manner to which therapeutic drug monitoring is conducted by pharmacists at present. While such an approach would be beneficial in expediting the return of diagnostic test results, it would only be valuable if sufficient funding were available from either government or private sources to cover the costs of relevant pharmacodiagnostic tests, and if sufficient evidence existed to justify funding such tests. Given the widespread concerns of pharmacists around the toxicities of

targeted therapies, a greater pharmacist involvement in using these tests could potentially help to ameliorate toxicities where such tests exist. Pharmacy education has a clear role to play in assisting any expanded role for pharmacists.

There is very little information in the literature regarding the present state of education around targeted cancer therapies in the United States, so it is difficult to compare Australian and American educational practices. Several authors, however, have examined American pharmacy education in pharmacogenomics, an area that is strongly associated with the area of targeted cancer therapies. The quality of pharmacogenomics education may be somewhat lacking. One survey in the United States reported that 32 out of 41 pharmacy schools and colleges taught pharmacogenomics, although the authors believed that there was room for improvement in the quality of education delivered.<sup>12</sup> Another study reported that 40 out of 46 American and Canadian pharmacy schools taught pharmacogenomics, which was a required part of the pharmacy course in 95% of these schools. However, 60% of respondents from these schools thought that this instruction was less than adequate.<sup>13</sup>

Gurwitz et al noted the importance of covering pharmacogenomics as part of oncology education.<sup>14</sup> Companion diagnostics for targeted cancer therapies incorporates pharmacogenomics, and based on the interview responses, it seems that diagnostics has been poorly covered in Australian and New Zealand pharmacy courses, with only 1 institution covering this area in any detail. Testing for trastuzumab and gefitinib was discussed at 1 institution; these drugs are among the very few with diagnostic tests required for PBS subsidy. Diagnostic tests in the context of results or restrictions set by the PBS were also discussed in pharmacy programs. As this present study did not investigate reasons as to why diagnostic tests were not covered by Australasian pharmacy courses, any reasons offered here would be purely speculative.

The notion that the burden of care with orally administered tyrosine kinase inhibitors falls onto patients is supported by existing observations in the literature.<sup>15-17</sup> Viele<sup>18</sup> and Winkeljohn<sup>19</sup> both support the idea of compliance diaries in assisting compliance with oral cancer therapies. This also was suggested by 1 clinical pharmacist in this study. In the United Kingdom, such an approach has already been tried with capecitabine, an orally administered pro-drug of 5-fluorouracil.<sup>20</sup> Pharmacists, having a professional expertise in medications, are obviously well placed to help improve compliance and assist patients in use of targeted therapies. One report notes that while there has not been any evaluation on whether pharmacists can affect patient compliance with oral cancer agents, pharmacists have significantly improved such compliance with



other types of therapy,<sup>21</sup> and both pharmacists and nurses have assisted with improving patients' medication compliance.<sup>22</sup> This gives further weight to the view that pharmacy education around targeted therapies is an important endeavour.

The primacy of experience in learning has been noted by a number of authors. Some believe that all learning is experiential learning,<sup>23</sup> while others believe that experiential learning is only 1 type of learning rather than a model of learning as a whole.<sup>24</sup> Nonetheless, the key message is the importance of experience in gaining and consolidating knowledge. Candy suggests that experiential learning is 1 of the approaches that is most likely to encourage students to garner skills that facilitate lifelong learning.<sup>25</sup> Furthermore, research at the University of South Australia indicates that the kinaesthetic modality of learning – essentially “learning by doing” – is used by pharmacy students.<sup>26,27</sup> The traditional didactic teaching model favored by pharmacy schools (all 9 academic staff reported using this to teach targeted therapies) does not necessarily cater to this learning modality. Other means of catering to students with kinaesthetic learning preferences include applications of the teaching material and “hands-on approaches.”<sup>28</sup> It may be worth exploring alternative educational models in order to appeal to the learning preferences of pharmacy students. Therefore, if any educational program on the fields of oncology and targeted therapies is constructed for pharmacy students, the role of experience rather than simply information exposure must be taken into account.

In this study, pharmacy academic staff members generally did not mention alternative educational models despite this question being specifically asked. Two novel models that were mentioned, however, were the wiki cases model and an interactive case-based approach. There is experience in the literature on using wikis, a collection of Web pages linked to one another where any user can edit any page, and the strengths of this approach include the potential for assisting in collaborative work between students.<sup>29</sup>

The second approach mentioned by an interviewee was an interactive case-based approach. Second Life (Linden Lab, San Francisco, California) is 1 means of presenting an interactive case-based approach. Second Life is a virtual world, where people operate through an “avatar” or a virtual representation of themselves,<sup>30</sup> and it has been used by Monash University in Victoria, Australia, to assist in teaching about tablet manufacturing and quality testing.<sup>31</sup>

The idea that only staff members with appropriate training or competencies should be involved in pharmaceutical care of patients receiving oral anti-cancer agents is echoed in the guidelines of the Society of Hospital Pharmacists of Australia (SHPA) for the provision of oral

cancer chemotherapy.<sup>32</sup> These guidelines, which specify agents such as imatinib and gefitinib as falling under this particular pharmaceutical category, also state that staff members without sufficient experience or knowledge should not manage the supply of such agents. The importance of continuing education and access to oncology education sources was stressed by some interviewees as well as by another set of SHPA guidelines.<sup>33</sup>

At a postgraduate level in the United States, pharmacists can obtain specialty residencies in oncology pharmacy practice accredited by the American Society of Hospital Pharmacists, and become certified as specialists in this area, through the Board of Pharmacy Specialties (BPS). Pharmacogenetics of anticancer agents is 1 of the topics that may be covered in the Oncology Pharmacy Specialty Certification Examination run by the BPS.<sup>34</sup> The importance of continuing education, particularly for pharmacists in the community setting or for those who have been in practice for many years, has been demonstrated.<sup>35</sup>

There were limitations to this study. While most interviewees were helpful and forthcoming in their responses, the questions asked of interviewees restricted deeper analysis of certain phenomena, particularly with pharmacy teaching issues, to be fully explored. For instance, reasons behind the general lack of either pharmacy teaching in pharmacodiagnostic tests or academic interest in alternative education models were not covered.

## CONCLUSIONS

Pharmacodiagnostic tests with the potential to assist in patient selection for targeted therapies may be underutilized due to a number of factors, including lack of experienced personnel to interpret these tests. Pharmacists, as healthcare professionals with particular expertise in drugs, could assist in the interpretation of these tests, similar to their established role in therapeutic drug monitoring. Pharmacists also are well positioned to assist patients with compliance with oral targeted therapies. While interviewees saw a certain degree of postgraduate training necessary for pharmacists to handle these drugs, undergraduate oncology education also was seen as being important.

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