Patient Preference for Aggressive Medication Therapies with Potentially Stronger Adverse Drug Reactions Revealed Using a Scenario-based Survey

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Some patients do not inform healthcare professionals of adverse drug reactions (ADRs) because they fear termination of aggressive medication therapies. Preferences for aggressive medication therapies may differ between patients and pharmacists. The goal of this study was to estimate whether pharmacists were able to accurately assess patient preference for aggressive medication therapies with potentially stronger ADRs. A cross-sectional study was conducted of hospitalized patients (35 to 74 years of age) receiving oral medications for a chronic disease or systemic chemotherapy at three hospitals in Japan. We estimated the extent of agreement between patient responses and pharmacist predictions using a scenario-based investigation (1) to examine the choice between an aggressive medication therapy and the standard therapy, and (2) to assess increased life expectancy as a result of aggressive medication therapy. The extent of agreement was estimated using the kappa statistic. Of 113 patients, 43 (38.1%) chose the aggressive medication therapy. Pharmacists correctly predicted the choice of 25 (58.1%) of these patients [kappa 0.32 (95% confidence interval 0.15–0.50)]. Of 111 patients, 42 (37.8%) expected one additional life expectancy year. However, pharmacists predicted that as many as 36 (85.7%) of these patients would require more years of added life expectancy before choosing an aggressive medication therapy [kappa 0.24 (0.08–0.40)]. Agreement between patients and pharmacists on the choice of aggressive medication therapy was generally poor. Pharmacists should make an effort to identify patients who might prefer more aggressive medication therapies with potentially stronger ADRs in order to minimize ADR risk.

Key words—patient preference; pharmacist; medication therapy management; communication; professional-patient relation; adverse reaction

INTRODUCTION

Patient perceptions and expectations of medication therapies1–5 can result in anxiety that can potentially influence the effectiveness and safety of these therapies. We have treated cancer patients who remained silent when they began to experience fatigue following rounds of chemotherapy.6 They were afraid the treatments would be terminated if potential side effects were revealed. It is important for healthcare professionals to have the ability to correctly determine patient preferences for aggressive medication therapies because these therapies are very likely to cause severe adverse drug reactions (ADRs) and, in some cases, can be life-threatening.

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Previous studies7–9 examining the association between patient and physician preferences for aggressive therapies showed quite a gap. However, to the best of our knowledge, there are no reports analyzing the gap at the individual level rather than the group level. There are also no other reports examining the gap between pharmacists and patients for aggressive medication therapies.

The goal of this study was to estimate whether pharmacists were able to accurately assess patient preference for aggressive medication therapies. We used scenario-based investigations to estimate the extent of agreement between patient responses and pharmacist predictions on an individual level (1) in choosing a new aggressive medication therapy with potentially stronger ADRs or a standard therapy and (2) on the number of added years of life expectancy

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to be gained as a result of the aggressive medication therapy. We also evaluated a variety of factors for an association with extent of agreement in the choice of therapy.

**METHODS**

**Participants** This cross-sectional study was conducted as part of the Medication Acceptance, Preference and Adherence Scale (MAPAS) studies. Participants in the present study are described in those reports. In brief, inclusion criteria of the studies were defined as hospitalized patients with chronic disease or chemotherapy who (1) were hospitalized at three hospitals (see below) from June 2009 to April 2010, (2) aged 35 to 74 years, (3) received pharmacist services such as medication counseling, and (4) had taken oral medications for a chronic disease (patients with chronic disease) or had received injectable systemic chemotherapy during their hospitalization (patients with chemotherapy). Exclusion criteria were defined as patients who had poor performance status in the activities of daily living (a score of four according to the Eastern Cooperative Oncology Group criteria), poor understanding of the instructions, difficulty conversing, received systemic chemotherapy other than injectable systemic chemotherapy, were due to be discharged within three days, or did not submit written informed consent.

This study was approved by the ethics committees at Tokushima Bunri University, Kagawa University, Takamatsu Red Cross Hospital, and Sakaide City Hospital, all of which are located in Kagawa prefecture in Japan.

**Measures** Pharmacists asked patients to respond to the following two questions using a flyer where a scenario was written. The first question (therapy choice) was ‘which therapy would you choose, the new aggressive therapy or the standard therapy, if you were a patient who has been diagnosed with two years of life expectancy?’ The effect of the standard therapy was set as a 50% chance of one added year of life expectancy, with slight to moderate ADRs (fatigue, nausea, decreased white blood cell and/or platelet count, and hair loss) with shock that would almost never develop. The effect of the aggressive therapy was also set at 50%, the same as the standard therapy, or potentially a little better. However, the magnitude of the ADRs (fatigue, nausea, decreased white blood cell and/or platelet count, and hair loss) was set as moderate or severe, including shock, but with a low probability of development (infrequent: 1 person/500 people). The second question (added life expectancy years) was ‘If you choose the aggressive therapy, how many added years of life expectancy would you anticipate as a result of that therapy?’

Pharmacists asked the questions during a face-to-face interview following the initial consultation. For patients receiving systemic chemotherapy, the questions were asked following completion of at least the first chemotherapy regimen. Pharmacists were also asked to predict patient responses to the questions.

Patient characteristics: sex, age, disease, injectable systemic chemotherapy, and hospitalization experience were obtained from medical records. Performance status; number of chronic oral medications; and ADR incidence, preceding hospitalization or during hospitalization prior to the interview, were obtained from medical records and/or interviews with pharmacists. Pharmacist characteristics: information regarding number of years as a pharmacist and previous charge of patients were provided by the pharmacists.

**Data Analysis** Extent of agreement between patient responses and pharmacist predictions was estimated using the kappa statistic. The kappa statistic shows the proportion of agreement that remains after chance has been excluded and is interpreted as follows: −1.00 (perfect disagreement), 0.00 (chance agreement), 0.01–0.40 (poor agreement), 0.41–0.74 (fair to good agreement), 0.75–0.99 (excellent agreement), and 1.00 (perfect agreement). The kappa statistic was tested based on the null hypothesis that the agreement is purely by chance. We estimated the approximate p-value for the test. We used unweighted kappa for nominal variables if estimating the extent of agreement regarding therapy choice. We used the quadratic weighted kappa for ordered variables if estimating agreement on added life expectancy years.

We also analyzed the factors associated with agreement for therapy choice using the Pearson chi-square test with exact p-value, as well as with therapy choice. All p-values were two-tailed with statistical significance defined a priori as p<0.05. We used SAS University Edition 9.04 (SAS Institute Inc., Cary) for estimation and test of the kappa statistic and used PASW statistical software 18.0 (IBM Corporation,
Armonk) for the other analyses.

RESULTS

Of patients who met the inclusion criteria, 131 hospitalized patients were enrolled, excluding 106 patients (30 for poor performance, 25 for poor understanding, 20 for planned discharge, 20 for inability to consent, 7 for difficulty conversing, and 4 for receiving chemotherapy other than injectable systemic chemotherapy). Of the eligible patients, 18 (13.7%) were excluded from the analysis of the present study because pharmacist predictions for their responses were not obtained. The remaining 113 (86.3%) were included in the analyses and their 13 pharmacists predicted their responses.

Table 1 displays patient and pharmacist characteristics. Patients aged 55 to 64 years and 65 to 74 years comprised approximately 35% of the 113 patients analyzed. Almost half of the patients had metabolic disease and about 30% received injectable systemic chemotherapy.

Table 2 displays patient therapy choices and pharmacist predictions of those choices. Of the 113 patients, 43 (38.1%) chose the aggressive therapy and 70 (61.9%) chose the standard therapy. Pharmacists correctly identified 25 (58.1%) of the 43 patients who chose the aggressive therapy. In total, there was a 68.1% agreement (n=77) between patient responses and pharmacist predictions. The unweighted kappa statistic was 0.32 (95% confidence interval 0.15–0.50, p<0.001), indicating poor agreement.

Figure 1 shows the years of added life expectancy patients expect from aggressive therapy vs. pharmacist predictions. We analyzed 111 of the 113 patients because we were not able to get pharmacist predictions for 2 patients. Forty-two (37.8%) patients expected only one additional year. However, pharmacists correctly predicted the choices of merely 6 (14.3%) of these patients. For the remaining 36 (85.7%) patients, pharmacists predicted that they would need more years of added life expectancy before they would choose the aggressive therapy; two years for 6 patients (14.3%), three years for 7 (16.7%), four years for 1 (2.4%), five years for 9 (21.4%), and six or more years for 12 (28.6%). One patient (2.4%) would not choose it at all. Notably, pharmacists predicted a considerably higher number of additional years when patients expected only one

| Disease                              | Patients | Pharmacists |
|--------------------------------------|----------|-------------|
| Metabolic disease                    | 56 (49.6)| 33 (70.6)   |
| Diabetes mellitus                    | 52 (46.0)| 44 (88.8)   |
| Hyperlipidemia                       | 17 (15.0)| 8 (16.7)    |
| Cardiovascular disease               | 40 (35.4)| 18 (36.3)   |
| Hypertension                         | 37 (32.7)| 21 (42.9)   |
| Respiratory disease                  | 4 (3.5)  | 4 (3.5)     |
| Endocrine disease                    | 4 (3.5)  | 3 (6.1)     |
| Blood disease                        | 12 (10.6)| 6 (12.2)    |
| Gastrointestinal disease             | 6 (5.3)  | 4 (8.1)     |
| Liver/gallbladder/pancreatic disease | 23 (20.4)| 15 (30.6)   |
| Hepatocellular carcinoma             | 10 (8.8) | 5 (10.2)    |
| Renal disease                        | 19 (16.8)| 15 (30.6)   |
| Renal failure                        | 13 (11.5)| 9 (18.3)    |
| Neuromuscular disease                | 6 (5.3)  | 4 (8.1)     |
| Gynecologic disease                  | 7 (6.2)  | 3 (6.1)     |

| Injectable systemic chemotherapy a |
|-----------------------------------|
| Yes                               | 36 (31.9)% |
| No                                | 77 (68.1)% |

| Performance status                |
|-----------------------------------|
| 0 (good)                          | 61 (54.0)% |
| 1–3 (poor)                        | 52 (46.0)% |

| Oral medication for chronic conditions |
|----------------------------------------|
| None                                   | 37 (32.7)% |
| 1–3 kinds                              | 31 (27.4)% |
| 4–6 kinds                              | 20 (17.7)% |
| 7–9 kinds                              | 16 (14.2)% |
| 10 kinds and more                      | 9 (8.0)%   |

| Incidence of ADR                      |
|---------------------------------------|
| None                                  | 60 (53.1)% |

| Hospitalization d                    |
|--------------------------------------|
| None                                 | 81 (71.7)% |

| Pharmacist n=13                      |
|--------------------------------------|
| Experience                           |
| <10 years                            | 6 (46.2)% |
| ≥10 years                            | 7 (53.8)% |

ADR: Adverse drug reaction. a Both primary disease and complication are included. b Injectable systemic chemotherapy during current hospital admission. c Malignant lymphoma 8 cases, urothelial cancer 5 cases, ovarian cancer 5 cases, pancreatic cancer 3 cases, breast cancer 3 cases, uterine corpus cancer 2 cases, myeloma 2 cases, colorectal cancer 2 cases, and 6 classified as other. d Does not include current hospital admission.
Table 2. Patient Preference vs. Pharmacist Prediction for Choice of Aggressive Therapy

| Pharmacist prediction | Aggressive therapy n=43, n (%) | Standard therapy n=70, n (%) |
|-----------------------|-------------------------------|-----------------------------|
| Aggressive therapy    | 25 (58.1)                    | 18 (41.9)                  |
| Standard therapy      | 18 (25.7)                    | 52 (74.3)                  |

Fig. 1. Choice of Aggressive Therapy: Patient Expectation of Additional Years of Life vs. Pharmacist Predictions

Not: would not choose. The reference line shows agreements between patient expectation of additional years of life and pharmacist predictions.

An agreement of 14.4% (n=16) was found between patient responses and pharmacist predictions, indicating poor agreement with a quadratic weighted kappa of 0.24 (95% confidence interval 0.08–0.40, p=0.005).

Among the surveyed patient characteristics, only the presence of renal disease was significantly associated with agreement of therapy choice [correct predictions for 18 (94.7%) of 19 renal disease patients vs. 59 (62.8%) of 94 patients without renal disease, p=0.006]. None of the remaining 16 patient characteristics (sex, age, diseases other than renal disease, chronic disease or chemotherapy, performance status, number of chronic oral medications, ADR incidence, and hospitalization) were significantly associated with agreement of therapy choice. As well, neither of the two pharmacist characteristics (years of experience and previous charge for patients) showed an association.

Table 3 shows the characteristics of 19 renal disease patients. Thirteen had renal failure with dialysis and 5 patients had urothelial cancer. With the exception of 2 patients, almost all chose the standard therapy. The choice of standard therapy by 17/19 (89.5%) renal patients was significantly higher than among patients without renal disease 53/94 (56.4%) (p=0.008). All patients with renal disease were covered by the same pharmacist, who correctly predicted the therapy choices of 18 (94.7%) patients.

A total of 13 pharmacists in this study covered 1 to 22 patients. Agreement with patient choice varied; the median of agreement for therapy choice was 83.3% (minimum–maximum, 0.0–100.0%) and the median of agreement for the added life expectancy years was 10.0% (0.0–50.0%). Pharmacists with a high proportion of agreement of therapy choice did not necessarily exhibit high agreement with years of added life expectancy.

**DISCUSSION**

This study addressed the discrepancy between patient preference for aggressive medication therapies with potentially stronger ADRs and pharmacist predictions of that choice, which statistical estimation showed were in poor agreement. Pharmacists were unable to identify up to 40% of the patients who preferred aggressive medication therapy. For as many as 85% of the patients who chose aggressive medication therapy, even if the effect was only one year of added life expectancy, pharmacists predicted that the patients would answer that more years would be needed before they would choose a more aggressive therapy. Pharmacists should be aware that the number of patients who prefer aggressive medication therapies, even with a small therapeutic effect and the possibility of stronger ADRs, may be higher than they would expect.

These results are supported by previous studies\(^7,9\) that compared the preference for aggressive therapies between groups of patients and physicians. A questionnaire study\(^7\) for patients with solid cancer found that 53.1% of patients accepted intensive chemotherapy even if the chance of a cure was only 1%. However, only 20.0% of medical oncologists and 12.4% of general practitioners accepted the chemotherapy. Another study\(^9\) of patients with endometrial cancer found that patients were willing to accept a lower minimally desired benefit than physicians when considering vaginal brachytherapy. The present study found that a discrepancy for the accep-
tance of aggressive therapies existed between patients and pharmacists as well as between patients and physicians, and proved the fact on an individual level. Patients do not necessarily talk about their conditions and the development of ADRs. Better monitoring can be achieved if pharmacists establish a better relationship with patients to engender more trust, which could ultimately motivate patients to confide more about adverse events.

The ability of pharmacists to accurately assess patient preference for aggressive medication therapies with potentially stronger ADRs should be developed to prevent patients from suffering severe or life-threatening ADRs. Further study is needed to develop a better way to distinguish between patients who do and do not prefer aggressive therapies and to develop methods of counseling where that preference is taken

| Patient | Therapy choice (aggressive) | Patient (pharmacist prediction)<sup>a</sup> | Added life expectancy<sup>b</sup> (Patient (pharmacist prediction)<sup>a</sup>) | Disease (Dialysis: types, period) | Sex | Age | Oral medication for chronic conditions | Incidence of ADR |
|---------|---------------------------|------------------------------------------|---------------------------------|---------------------------------|-----|-----|-------------------------------------|------------------|
| 1       | Standard (standard)       | 3 years (2 years)                        | Renal failure (P, ≥5 years)     | Male                            | 65–74 years | 7–9 types | Yes |
| 2       | Standard (standard)       | 3 years (2 years)                        | Renal failure (P, ≥5 years)     | Male                            | 55–64 years | ≥10 types | Yes |
| 3       | Standard (standard)       | Would not choose (5 years)              | Renal failure (H, ≥5 years)     | Female                          | 55–64 years | 4–6 types | Yes |
| 4       | Standard (standard)       | 3 years (2 years)                        | Renal failure (H, 1–4 years)    | Male                            | 65–74 years | 7–9 types | Yes |
| 5       | Standard (standard)       | 3 years (2 years)                        | Renal failure (P, 1–4 years)    | Male                            | 65–74 years | 4–6 types | Yes |
| 6       | Standard (standard)       | 4 years (3 years)                        | Renal failure (P, 1–4 years)    | Male                            | 65–74 years | 1–3 types | Yes |
| 7       | Standard (standard)       | 3 years (2 years)                        | Renal failure (P, 1–4 years)    | Male                            | 55–64 years | ≥10 types | Yes |
| 8       | Standard (standard)       | 2 years (5 years)                        | Renal failure (H, 1–4 years)    | Female                          | 65–74 years | ≥10 types | Yes |
| 9       | Standard (standard)       | 2 years (3 years)                        | Renal failure (H, 1–4 years)    | Female                          | 35–54 years | 7–9 types | Yes |
| 10      | Standard (standard)       | 5 years (3 years)                        | Renal failure (P, <1 year)      | Male                            | 65–74 years | 1–3 types | No  |
| 11      | Standard (standard)       | 2 years (2 years)                        | Renal failure (H, <1 year)      | Female                          | 65–74 years | 4–6 types | Yes |
| 12      | Standard (standard)       | 3 years (2 years)                        | Urothelial cancer (chemotherapy)<sup>c</sup> | Male                            | 65–74 years | —       | Yes |
| 13      | Standard (standard)       | 3 years (2 years)                        | Urothelial cancer (chemotherapy)<sup>c</sup> | Male                            | 65–74 years | —       | Yes |
| 14      | Standard (standard)       | 3 years (5 years)                        | Urothelial cancer (chemotherapy)<sup>c</sup> | Male                            | 65–74 years | —       | Yes |
| 15      | Standard (standard)       | 2 years (3 years)                        | Urothelial cancer (chemotherapy)<sup>c</sup> | Male                            | 55–64 years | —       | Yes |
| 16      | Standard (standard)       | 2 years (3 years)                        | Urothelial cancer (chemotherapy)<sup>c</sup> | Female                          | 55–64 years | —       | Yes |
| 17      | Standard (standard)       | 2 years (3 years)                        | Prostatic cancer (chemotherapy)<sup>c</sup> | Male                            | 65–74 years | —       | Yes |
| 18      | Aggressive (aggressive)  | 1 year (3 years)                         | Renal failure (H, ≥5 years)     | Male                            | 35–54 years | ≥10 types | Yes |
| 19      | Aggressive (standard)     | 1 year (3 years)                         | Renal failure (P, <1 year)      | Female                          | 35–54 years | 7–9 types | No  |

ADR: Adverse drug reaction, P: Peritoneal dialysis, H: Hemodialysis. <sup>a</sup> Same pharmacist covered all patients with renal diseases. <sup>b</sup> Added life expectancy that patient expected as an effect of aggressive medication therapy. <sup>c</sup> Injectable systemic chemotherapy.
into consideration. Because the present study showed that the presence of renal disease was the only factor associated with agreement between patients and pharmacists, one approach may be to attain a full understanding of disease characteristics and the psychological changes that can occur in patients with those diseases.

In the present study, many of the renal disease patients suffered renal failure with dialysis. The majority of these patients chose standard therapy. The characteristics of renal failure and the psychological and emotional profiles of these patients, which include distress over dialysis treatment, disease progression, the large number of required oral medications, and experience of burdensome ADR would probably make them choose the standard therapy. An understanding of these characteristics and profiles may have resulted in the high percentage of agreement between the pharmacist and the patients. Also the fact that all of the renal disease patients had the same pharmacist may have been a factor of the high agreement.

This study has some limitations. First, a scenario was used to investigate patient preference. Patients may give different responses from those in this study if they actually encounter the proposed situation. Second, the study population may have contained disease bias, as the patients were restricted to the wards in which pharmacists who cooperated with the study were assigned. Additionally, each pharmacist covered a minimum of at least one patient. Therefore, agreement proportion per pharmacist should be prudently interpreted, as well as the results that pharmacist characteristics such as years of experience did not influence agreement of therapy choice. Third, regimen and therapy procedures may have changed since the investigation period (2009 to 2010). Accordingly, it is possible that different results may be achieved if the investigation were conducted today. However, there are very few studies in Japan that focus on the patient perspective for medication therapies from the pharmacist viewpoint.19–21) The findings in this study can be valuable in finding methodologies to improve the communication and relationship between patients and pharmacists and to secure patient safety.

This study concludes that agreement was poor between patient preference for aggressive medication therapies and pharmacist predictions of that choice. Pharmacists should make an effort to identify patients who might prefer more aggressive medication therapies with potentially stronger ADRs.

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