Disparities and Challenges in Adherence to Oral Antineoplastic Agents

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OVERVIEW

The issue of medication noncompliance is becoming increasingly important in oncology as more cancer therapies are delivered orally. Medication adherence is difficult to assess and there is no gold standard of measurement. The act of measuring adherence can affect outcomes. Medication noncompliance is common, and is estimated to be 50% in treatment of chronic diseases. Studies have shown that women initiate adjuvant hormonal therapy for breast cancer 64% to 88% of the time when prescribed. Of those who initiate therapy, 50% to 80% are adherent for the prescribed duration, depending on the study. Patients noncompliant with adjuvant hormonal therapy for breast cancer have worse overall survival than their counterparts. Suboptimal treatment responses in chronic myeloid leukemia (CML) are also associated with medication noncompliance. Poor adherence can also affect clinical trial results, leading to inaccuracies of treatment efficacy. Barriers to compliance can occur on the individual, cultural, or system level. Examples of specific barriers are side effects, cost and access to medication, and individual health beliefs. Specific populations, including racial minorities, elderly patients, and very young patients, may be at higher risk for medication noncompliance. Strategies to improve compliance are multifactorial and include improvement of patient education, reduction of treatment side effects, interventions to alter behavior, and changes in public policy to improve financial barriers to treatment. Technology has been an effective tool in improving compliance in noncancer-related illness, and ongoing studies are evaluating its role in the oncology population.

Oral cancer therapeutics are becoming a mainstay for treatment of a variety of cancers. As cancer therapies shift from the infusion room to a pill, the issue of patient compliance is being recognized as increasingly important in oncology practice. Much of what is known about noncompliance is from studies on patients with chronic conditions such as hypertension, HIV, and pulmonary tuberculosis.1-2 It is estimated by the World Health Organization that only half of patients in industrialized countries are compliant with their treatment.3 When prescribed an oral medication many patients fail to fill the prescription (noninitiation), fail to take the drug as prescribed (nonadherence), or fail to continue long-term usage of the medication (early discontinuation) (Table 1). Furthermore, medication noncompliance is associated with treatment failure and increased health care expenditures.1-3 Vulnerable patients are often more likely to have difficulty with compliance, which in turn may lead to disparities in treatment outcomes. This review will focus on compliance to oral cancer treatments including the influence of noncompliance, methods of assessing compliance, barriers to compliance, and possible solutions.

HOW DO WE MEASURE COMPLIANCE?

There is no gold standard in assessing compliance. Table 2 demonstrates available methodologies along with their potential pitfalls. It should also be noted that the act of measuring compliance may also influence the behavior of participants and alter outcomes (The Hawthorne Effect).4 When participants know that their compliance is being monitored they may become more compliant than if they were not being monitored. Indirect measures can be inaccurate, cumbersome, or manipulated by the patient. These measures include review of pharmacy or insurance data that does not capture all patients and provides no information about correct dosing. Patient self-reports and patient diaries can be used, but patients may overestimate their compliance to please their physicians.4
Direct methods of measuring compliance may be more accurate but are more time consuming and expensive. In addition to direct observation, other direct methods include measurement of metabolites or biomarkers in the patient’s blood or urine. Again, these methods are expensive and metabolites can vary by an individual’s metabolism. In addition, patients are more likely to be compliant with their regimen before a doctor’s visit, so testing methods would not take into account a patient’s intermittent use of medication. These methods may also complicate the physician-patient relationship as patient may perceive these methods to indicate lack of trust by their provider.

### TABLE 2. Methods of Measuring Adherence

<table>
<thead>
<tr>
<th>Measure</th>
<th>Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Measures</td>
<td></td>
</tr>
<tr>
<td>Directly observed therapy</td>
<td>Labor intensive and time consuming. Patients can hide pills in their mouth</td>
</tr>
<tr>
<td>Metabolites (urine and/or blood)</td>
<td>Pharmacokinetics are variable between patients. Patients are more likely to take medication prior to physician visit and may not be representative of true adherence. Expensive.</td>
</tr>
<tr>
<td>Biomarker</td>
<td>Expensive and invasive.</td>
</tr>
<tr>
<td>Indirect Measures</td>
<td></td>
</tr>
<tr>
<td>Self-report</td>
<td>Volunteer bias (those that answer are more likely to be compliant).</td>
</tr>
<tr>
<td></td>
<td>Patients do not always admit to noncompliance. Recall errors.</td>
</tr>
<tr>
<td>Electronic pill bottles</td>
<td>Expensive. May change behavior.</td>
</tr>
<tr>
<td></td>
<td>May not always correlate with adherence.</td>
</tr>
<tr>
<td>Pill counts</td>
<td>Labor intensive. No information regarding correct dosing times.</td>
</tr>
<tr>
<td></td>
<td>Patients can discard pills, which would alter results.</td>
</tr>
<tr>
<td>Pharmacy or insurance data</td>
<td>All patients are not captured.</td>
</tr>
<tr>
<td></td>
<td>Patients may obtain medication by another source. Unclear intent.</td>
</tr>
<tr>
<td>Clinical response</td>
<td>Many confounding variables.</td>
</tr>
<tr>
<td>Patient diaries</td>
<td>May not represent the truth.</td>
</tr>
</tbody>
</table>

Table adapted from Osterberg et al.¹

These methods also rely on patient’s memory and recall abilities. Pill counts are also an option, but are cumbersome to the performer and can also be manipulated by the patient. Electronic pill bottles are expensive and also do not provide information that the patient has actually ingested the medications.

**KEY POINTS**

- As oral therapies for cancer are becoming more common, it is increasingly important to recognize and assess for noncompliance in the proper use of medication in our clinical practice.
- The optimal method of measuring compliance is unknown; all methods have limitations and the act of measuring compliance can affect behavioral outcomes.
- Medication noncompliance is associated with higher costs of care and worse clinical outcomes.
- Vulnerable populations are more likely to be noncompliant with oral therapy, and this may lead to disparities in outcomes.
- Novel strategies to improve compliance to oral antineoplastics are needed at both the individual and the health-policy level.

**SCOPE OF THE PROBLEM**

Compliance challenges have been well described in the literature, but primarily for noncancer-related illnesses. In the treatment of HIV, poor compliance is linked to worse outcomes. World-wide compliance of patients with HIV ranges from 37% to 83% depending on the treatment methods used and the patient population studied. A quarter of patients with hypertension fail to achieve favorable blood pressure control. Poor medication compliance has been identified as the number one cause of this problem. In fact, 50% of patients labeled as having refractory hypertension are actually noncompliant with their therapy. Patients with psychiatric disease also struggle with compliance: it is estimated that adherence to antidepressants ranges from 40% to 70%, compliance with antipsychotic medication for patients with schizophrenia ranges from 50% to 60%, and for those with bipolar disorder can be as low as 35%.¹³⁻⁷

Much of what is known about compliance in oncology comes from the study of hormone therapy in the adjuvant treatment of breast cancer. With regard to initiation of therapy, a study was performed in 13,753 women with hormone-receptor (HR) positive breast cancer diagnosed from 1996 to 2007. Initiation of therapy was defined by pharmacy-record review as women who filled prescriptions for hormone therapy within one year of their diagnosis. It was found that of this population of women, only 70% of women initiated the prescribed hormone therapy.² Similarly, Kimmick et al.⁶ analyzed the North Carolina Cancer Registry-Medicaid linked data set and found that only 64% of women with hormone-positive early-stage breast cancer that were prescribed hormone therapy filled a prescription for hormone therapy within one year of diagnosis. It is clear that the patient population and method of assessment influence these numbers. In a prospective study of 725 women with HR-positive breast cancer, hormone therapy was not initiated by 17.9% of patients when measured by medical-record review and 12.0% of patients when measured by patient self-report.⁷

With regard to adherence to hormone therapy in those that initiated medication, one of the reports used New Jersey Medicaid data. The investigators found that overall adherence was 77% and that adherence fell to 50% in the fourth year of treatment.⁸ In this study patients were considered adherent if they had a medication possession ratio (MPR)
greater than 80%. MPR is defined as the number of pills dispensed divided by the total number of days in the period evaluated. Subsequently these findings were confirmed in a larger study of 8,769 women with HR-positive women with early-stage breast cancer from the Kaiser Permanente database. Adherence was also defined as a MPR greater than 80%. This study found that of the group of women who initiated therapy, 32% discontinued treatment early. Of those who continued with treatment, 28% were nonadherent to the treatment plan at some point. Therefore, only 49% were adherent for the full duration of therapy. Kimmick et al., in their previously mentioned study, reported that within the year after a initial prescription was filled adherence was 60% and persistence was 80%. The aforementioned studies were based on administrative data and, as such, the reasons for noncompliance were not reported.

Our knowledge about noncompliance is not limited to hormone therapy. The Cancer and Leukemia Group B performed a randomized study (49,907) of women age 65 and older with early-stage breast cancer administering standard intravenous chemotherapy or oral capcitabine. The women randomly assigned capcitabine were asked to participate in a companion study to monitor adherence. Of the eligible 633 patients in the capcitabine arm, 161 were enrolled to the adherence study. Adherence was assessed by using a microelectronic monitoring system installed in the pill bottle that recorded the opening of the pill bottle. This study found that 77% of participants were persistent with their therapy to completion. Twenty-five percent of participants randomly assigned to take capcitabine were nonadherent with their therapy. Overadherence was seen in 11% of participants. Similarly, a multi-institutional study performed in Belgium evaluated patients with CML over 90 days to assess their compliance to imatinib. Adherence was measured by patient interview and pill counts. It was reported that approximately 36% of patients were nonadherent to therapy at some point, and only 14% were compliant 100% of the time. In both of these studies, it should be noted that participants were aware their medication compliance was being measured, which may have increased compliance, making this data not truly representative of “real world” compliance.

**IS THERE A RELATIONSHIP BETWEEN COMPLIANCE AND OUTCOME?**

Hospitalizations in the United States related to medication noncompliance cost an estimated $100 billion dollars annually and account for 33% to 69% of medication-related hospitalizations. Along with increased costs to the health care system, medication noncompliance is associated with worse clinical outcomes; however, this may not only reflect the efficacy of the treatment but also other health behaviors of compliant patients. It was noted that patients participating in placebo-controlled clinical trials who were noncompliant with the placebo had worse clinical outcomes. The Coronary Drug Project was a randomized controlled trial to evaluate mortality effect of lipid-lowering drugs in men after a myocardial infarction. In patients who were randomly assigned clofibrate as treatment and were adherent to their medication had a lower 5-year mortality rate compared with those who were nonadherent (15% vs. 25%). In patients randomly assigned to receive the placebo, it was also found that adherence to the placebo was associated with a lower 5-year mortality rate (15% vs. 28%). Adherence to the placebo was also seen have a mortality benefit in the Beta Blocker Heart Attack Trial (BHAT). Among patients randomly assigned to the placebo arm, the mortality rate was 3.0% in adherent patients and 7.0% in nonadherent patients.

Development of drug resistance has been seen in noncompliant patients with both HIV and pulmonary tuberculosis and has been seen in patients noncompliant with their oral antineoplastic medication. Sandoval et al. reported a case of a pediatric patient with CML who was noncompliant with imatinib therapy who subsequently developed resistant disease attributed by her doctors to medication noncompliance. Observational studies suggest that noncompliance with adjuvant hormone therapy for early-stage breast cancer is associated with worse outcomes. Yood et al. found that in a study of 886 patients age 65 or older with early-stage, hormone-positive breast cancer taking tamoxifen, women treated for less than 1 year had higher rates of death compared with those treated for the suggested 5 years (hazard ratio 6.26, 95% CI 3.1-12.64). Similarly, in an observational study of patients treated at Kaiser Permanente, it was found that a medication-possession ratio equal or greater than 80% was associated with a better 10-year overall-survival rate; 81% who continue for prescribed duration vs. 74% who discontinued therapy early (p < 0.0001). With regard to the treatment of CML, noncompliance with imatinib therapy is associated with poorer outcomes, increased health care costs, and development of treatment resistance. Noens et al. reported that patients with suboptimal responses (incomplete hematologic response at 3 months, less than partial cytogenetic response at 6 months, and less than major molecular response at 18 months) were in the higher percentage of patients who were nonadherent (23.2% ± 23.8%) compared with those with optimal responses (7.3% ± 19.3%). Among patients with a complete cytogenetic response, less patients were nonadherent (measured by patient and family interviews and pill counts) than those with an incomplete cytogenetic response (9.1% ± 18.1% vs. 23.9% ± 19.2%, p = 0.004). When compliance is measured with pharmacy reports and patient interviews, 29.6% of patients were noted to be noncompliant at some point during their treatment, and 5-year event-free survival was improved for patients compliant with imatinib (76.7% vs. 59.8%, p = 0.011). Achievement of complete cytogenetic response was statistically more likely in patients who were compliant with therapy (47% vs. 27%, p = 0.001).

Poor compliance can also influence the power to detect a difference between groups in clinical trials. If patients are nonadherent or noncompliant with study regimens, efficacy may be falsely low. Two recent studies, ATLAS (Adjuvant
Tamoxifen, Longer Against Shorter)\textsuperscript{19} and aTTom (adjuvant Tamoxifen – To offer more)\textsuperscript{20} have been evaluating extended therapy with tamoxifen from 5 years to 10 years. The results are conflicting: the ATLAS study shows benefit of extended tamoxifen treatment and the aTTom study shows no benefit. Interestingly, adherence with hormone therapy has been noted to be approximately 80% in both studies, suggesting that full clinical benefit of extended tamoxifen treatment may not have been appreciated because 20% of participants are not actually taking the drug.

**WHY ARE PATIENTS NONCOMPLIANT?**

Barriers to compliance include patient-, physician-, medication-, and system-related variables. Known barriers include medication side effects, cost and access to medications, patient behaviors, and education. Poor compliance is usually associated with a combination of these factors.\textsuperscript{2} In general, therapy that requires a higher degree of change to one’s behavior or normal routine increases the risk of non-compliance. It is also been observed that compliance with long-term therapy diminishes after 6 months of initiation.\textsuperscript{1,2}

Poor adherence may also be a sign of poor drug tolerability and increased sided effects that are not accurately reported in the literature if patients are noncompliant. For example, Sonpavde et al.\textsuperscript{21} evaluated oral sunitinib for treatment of castration-resistant prostate cancer. Common side effects included fatigue, anemia, nausea, anorexia, and neutropenia. Although severe grade 3–4 toxicities were infrequent, more than half of the patients (52.8%) discontinued therapy because of side effects.

A variety of observational studies have assessed predictors of nonadherence in patients prescribed adjuvant hormone therapy for early-stage breast cancer and are summarized in Table 3. In three studies\textsuperscript{8-9,22} extremes of age, race, and increased number of comorbidities were associated with non-adherence. Other factors associated with poor adherence are prescriptions written by nonmedical oncologists,\textsuperscript{8,22} being single,\textsuperscript{9} number of total prescriptions,\textsuperscript{22} lack of adjuvant radiation or chemotherapy,\textsuperscript{9} and higher copays.\textsuperscript{22}

It is also important to consider direct costs to patients as antineoplastic drugs are expensive. For example, it is estimated that monthly patient costs of sunitinib is $7,945 USD and $6,990 USD for sorafenib.\textsuperscript{23} An 8-week cycle of everolimus is estimated to cost $10,399 USD.\textsuperscript{24} Even for patients with prescription drug benefits, out-of-pocket expenses can add up with costly copayments. Neugut et al.\textsuperscript{22} preformed a study by using a pharmacy and medical claims database from Medco Health Solutions of women prescribed adjuvant aromatase-inhibitor therapy. They found an inverse association between copayment amount and patient adherence. In women age 65 or older, a copayment of $30 to $89.99 for a 90-day prescription was associated with decreased persistence. In all of the women studied, a copayment of $90 or greater was associated with less persistence.

Another important barrier to compliance, which is more difficult to measure, are patients’ beliefs. Patient’s expectations may affect medication compliance. An individual who believes that they can control the events in their life may have better adherence to a medical regimen, as they believe that their behavior affects their health.\textsuperscript{3} Other individuals, who believe that their destiny is determined by factors out of their control may be less adherent with their medication. Patients who believe that the medical therapy will be effective against their disease are more likely to initiate therapy than those who believe the regimen will not work.\textsuperscript{4}

**DISPARITIES AND COMPLIANCE**

There are significant racial- and age-related disparities in the delivery of cancer care, specifically in breast cancer treatment. Racial minorities, individuals with lower socioeconomic status, and elderly patients are less likely to receive optimal adjuvant therapies. Once treatment is initiated, patients in these groups are less likely to complete the full courses of therapy,\textsuperscript{25-27} and this may contribute to the known disparities in outcome. Low-income women studied that appear in the North Carolina Cancer Registry-Medicaid database initiated adjuvant hormone therapy for breast cancer only 70% of the time.\textsuperscript{9} In Dr. Partridge’s study\textsuperscript{8} of tamoxifen adherence by using data from the New Jersey Medicaid Database found that women younger than age 45 (OR = 2.61), older than age 85 (OR = 1.87), and who are nonwhite (OR = 1.62) were more likely to be noncompliant with adjuvant hormone therapy. Results from Dr. Hershman’s review of the Kaiser Permanente database\textsuperscript{9} correlated with these findings. By multivariate analysis, women younger than age 50 (OR = 1.27) and older than age 65 (OR = 1.10) were more likely to
discontinue hormone therapy. Black women were more likely to be nonadherent to therapy (OR = 1.23). Noncompliance within these groups may explain some of the disparities in outcomes.

**HOW DO WE IMPROVE COMPLIANCE?**

It is clear that there is a need for novel approaches to improve medication compliance. Classically, interventions to improve compliance are based on improving patient education, simplifying medication regimens, improving communication between patient and medical staff, and by using cues to remind patients of dosing schedules. These interventions rely on a multidisciplinary team to succeed. Even with the best of intentions the effects of these interventions lessen with time.

**Patient Education**

Educational interventions for patients and/or their family members can improve compliance. Interventions can range from distributing written materials, lectures, and discussions ranging from a single session to multiple structured sessions. A randomized study performed in Korea of patients with chronic phase CML prescribed imatinib asked patients to partake in either a counseling program or to receive standard care. Those assigned to the counseling program received phone consultations by a nurse, daily text messaging reminders to take imatinib, and others received other forms of written communication by their medical team. Those who participated in the counseling program were compliant 93.0% of the time compared with patients receiving standard care who were compliant 76.2% of the time (p = 0.001).

**Reduce Side Effects**

It has been noted that in treatment of psychiatric illness, medications with fewer side effects have higher rates of persistence and adherence. Providers should ask patients on oral regimens about side effects or barriers to compliance. If side effects are present, a plan should be developed on how to minimize and treat these effects. For example, if patients are aware of the benefits of selective serotonin release inhibitor in management of tamoxifen-related hot flashes, they may be more likely to continue the medication when side effects arise.

**Behavioral Interventions**

Technology, in combination with the above interventions, may play an increasingly important role in medication compliance. Cellular-telephone ownership and text-messaging use has increased significantly over the past decade. As noted previously, Moon et al. found that patients with chronic phase CML who received counseling and daily text messaging reminders to take imatinib were more compliant than those who did not receive these interventions. In the treatment of HIV, patients who received weekly text message reminders were more compliant with antiretroviral therapy than those who did not receive these alerts.

Behavioral interventions such as electronic reminders appear to be an effective tool to enhance medication compliance in the treatment of chronic diseases. Ongoing clinical trials are currently evaluating the benefits of these approaches in the oncology-patient population, including a randomized SWOG study in which women with early-stage HR-positive breast cancer prescribed aromatase inhibitor therapy are to receive twice-weekly reminder text messages compared with usual care. The primary end point is hormone therapy discontinuation.

Other behavioral interventions, such as automatic pharmacy refills and electronic prescribing may also improve compliance in this population.

**Public Policy**

As mentioned earlier, antineoplastic therapy can be expensive, and treatment with oral agents may be associated with higher out-of-pocket costs, even for those with prescriptions benefits. However, it is known that medication noncompliance can be very costly to the health care system since it is associated with increased physician visits, hospitalizations, and longer lengths of stay. Medication compliance can possibly be improved if financial barriers to medical therapies are improved. Future public health efforts are needed to ensure access to effective therapies for cancer.

**CONCLUSION**

Noncompliance with therapy (noninitiation, nonpersistence, nonadherence) is a common problem in the treatment of patients with cancer with oral antineoplastics. Noncompliance with medical therapy affects the efficacy of therapy and is associated with worse outcomes. Apart from noncompliance, certain groups are at higher risk of receiving suboptimal care and members of these groups may be more noncompliant with therapy. It is important to recognize nonadherence and care disparities in our clinical practice and to focus on high-risk individuals to improve patient compliance. Phase III clinical trials investigating oral antineoplastics should assess compliance, as this can alter outcomes and affect therapy for “real world” patients. Further investigation is needed to determine the role of noncompliance in cancer resistance, particularly in endocrine therapy.

**Disclosures of Potential Conflicts of Interest**

The author(s) indicated no potential conflicts of interest.