

Adherence to Therapy With Oral Antineoplastic Agents

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With the rise in availability and increasing use of oral anti-cancer agents, concerns about adherence to prescribed regimens will become an increasingly important issue in oncology. Few published studies have focused on adherence to oral antineoplastic therapy, in part because the vast majority of chemotherapy is delivered intravenously in physicians' offices or hospitals. In this article, we review current knowledge of adherence behavior with regard to oral medications in general, including factors associated with adherence and methods for measuring adherence. We also review published studies of adherence to oral antineoplastic agents in adult and pediatric populations and adherence issues in cancer prevention. The available evidence reveals that patient adherence to oral chemotherapy recommendations is variable and not easily predicted. Adherence rates ranging from less than 20% to 100% have been reported, and certain populations, such as adolescents, pose particular challenges. Future efforts should focus on improving measurement and prediction of adherence and on developing interventions to improve adherence for both patients in clinical trials and patients being treated outside of the research setting. Assessment of adherence among individuals with cancer and implementation of interventions in situations of poor adherence should improve clinical outcomes. [J Natl Cancer Inst 2002;94:652-61]

The use of orally administered anticancer therapy is likely to increase dramatically in the coming years. Agents such as tamoxifen, prednisone, and oral cyclophosphamide have long been part of the management of many malignancies. More recently developed oral chemotherapy formulations include fluorouracil derivatives, idarubicin, etoposide, vinorelbine, oral taxanes, and fludarabine. New oral drugs have shown promise in early clinical trials (e.g., STI-571 for chronic myelogenous leukemia), and many other novel agents are administered orally. Oral agents also have a dominant role in the evolving field of chemoprevention of malignancies, where oral administration may improve efficacy in some settings by facilitating chronic exposure to the drug.

Because oral counterparts of intravenous (IV) agents may have different side-effect profiles, they may be better tolerated in some circumstances (1). Furthermore, as oncologists pay more attention to patient preferences and quality-of-life issues in clinical care, treatment options that enhance flexibility for patients are likely to be used more often. There is little question that oral regimens are more convenient for patients, and initial research (2) reveals that patients prefer oral to IV chemotherapy, so long as efficacy is not compromised.

Although oral chemotherapy has many potential benefits, there are two areas of great concern: 1) bioavailability and 2) patient adherence (3). Pharmacologic manipulations can often

ameliorate concerns about bioavailability. For instance, the addition of an oral inhibitor of dihydropyrimidine dehydrogenase has a dramatic effect on the pharmacokinetics of orally administered 5-fluorouracil (4-6). Oncologists seldom consider the issue of adherence because of the widespread use of IV chemotherapy, which is traditionally administered in a clinic setting. Yet suboptimal adherence may prove to be the greatest barrier to the effective use of new oral agents, particularly if oncologists fail to consider this potential obstacle (7). In addition, effective methodologies to evaluate adherence in individual patients are limited. In an effort to illuminate this complex issue and to guide researchers and health care providers to improve patient care and outcomes, we review the current knowledge of adherence behavior with oral medications in general. We also review the published studies of adherence to oral antineoplastic therapies in adult and pediatric populations and adherence issues in cancer prevention, and we provide recommendations for patient care and future research.

THE IMPORTANCE OF ADHERENCE

Adherence (often referred to as compliance) can be defined as the extent to which a patient's behavior coincides with medical advice (8). Adherence to any intervention over long periods is determined largely by the individual's perception of the risks, benefits, and costs of the intervention (9). Costs, in this sense, include not only economic outcomes but also the potential toxic effects of therapy. The psychosocial implications of taking medication(s) on an ongoing basis and the logistic demands of such treatment must also be considered. Adherence rates for many long-term drug therapies have been shown to be strikingly low, often no more than 40%-50% (10-12). Clinicians generally assume that patients are taking drugs as prescribed and, if they discuss the topic with their patients at all, believe their patients when they say they are taking their medications as prescribed.

Cancer patients are generally thought to be highly motivated by the gravity of their disease, with "too much to lose" by being nonadherent (13). Yet adherence to other treatment programs that are documented to reduce mortality or the risk of other catastrophic outcomes (e.g., statins prescribed after myocardial infarction) is poor (14-16). Subjective estimates of adherence by physicians and nurses are unreliable for assessing patients'

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medication use, with clinicians often failing to detect markedly poor adherence to prescribed regimens (17,18). Even when health care providers are aware of potential nonadherence problems, they have been found to be unable to predict correctly which patients will adhere to therapy (19).

Adherence to treatment is a complex and multifaceted issue that can substantially alter the outcomes of therapy (19). Nonadherence can contribute greatly to the variability observed in a drug's therapeutic effect if the clinician incorrectly attributes the patient's worsening condition to an absence of drug activity (14). This erroneous conclusion may lead to unnecessary diagnostic testing, hospitalizations, and changes in dose or regimen. Nonadherence has also been associated with an increase in physician visits, higher hospitalization rates, and longer hospital stays (10,20–22). In a clinical trial, nonadherence can lead to misleading results, inconsistent response rates, and potentially erroneous dosing recommendations (19,23–25). Finally, suboptimal adherence can compromise the patient–provider relationship, because misconceptions about the effects of a therapy on the part of either the patient or the provider may lead to a breakdown in communication and negatively affect the patient's views about care (13).

Another frequently overlooked problem—and one that may be more of an issue in the care of oncology patients than of other patients—is overadherence to self-administered medication. A “more is better” approach, or confusion resulting in overuse of a drug, has been documented in studies of other diseases (26,27) and may, in the case of oral chemotherapy, lead to substantially increased toxicity. Dosing schedule is an important factor in the effectiveness of some chemotherapeutic agents, and taking drugs more or less frequently than prescribed may affect therapeutic efficacy. Furthermore, the degree of adherence required to achieve the desired treatment goal is likely to vary from one regimen to another. In particular, the half-life of an oral agent has a large effect on the degree of nonadherence that can be tolerated without compromising outcome. A classification scheme of adherence behavior has been proposed that consists of six different behavior types: adherer, partial adherer, overuser, erratic user, partial dropout, and dropout (28). Adherence can be viewed as a continuum from fully adherent to totally nonadherent, with most patients falling somewhere in between (29).

Few studies of cancer patients have evaluated the relationship between adherence levels and achievement of the treatment goal. In a retrospective analysis, Bonadonna and Valagussa (23) found that breast cancer patients who received 85% or less of their prescribed adjuvant chemotherapy had shorter relapse-free and total survival times than those who received more complete treatment. Patients who received less than 65% of planned therapy showed markedly inferior disease-free survival. In prospective trials (30–32) the administration of lower-than-standard IV doses has been shown to compromise disease outcomes. Physician adherence to scheduled dosing and timing of chemotherapy has been associated with improved survival rates among children with acute lymphoblastic leukemia (33). Among women with early-stage breast cancer, the benefits of tamoxifen are greater with 5 years of therapy than with only 1 or 2 years (34,35). It is unclear, however, whether these data on tamoxifen—the adherence equivalent of total dropout after 1 or 2 years—can be extrapolated to other situations of nonadherence, including long breaks in therapy or frequent dosing omissions.

PREDICTING ADHERENCE

Adherence to treatment depends on many factors, and no simple explanation for nonadherence exists. Potential determinants of adherence include sociodemographic characteristics, specific aspects of the treatment regimen (type, complexity, side effects, and duration), and features of the illness or potential illness (symptoms, duration, disability, and medically defined seriousness) (36). Although many of these factors are often easily identified and measured, the literature assessing their relationship to adherence has been inconsistent (36,37). Some investigators have criticized this “medical approach” to predicting adherence, arguing that results of such studies are inconsistent because behavioral determinants, which are much harder to measure, are more important than medical factors in predicting adherence (29,36,38).

Some researchers have used the “health belief model” to explain patient adherence (36,37,39). This model, originally formulated to predict acceptance of preventive services, relates patients' perceptions of the seriousness of their illness and the efficacy of its treatment with their adherence to prescribed therapy (36,39,40). The health belief model contains the following elements: 1) the individual's evaluation of his or her health condition, including disease severity and his or her own perceived vulnerability or sensitivity to the disease state; 2) the individual's evaluation of the risks and benefits of the advocated health behavior—in this case, adherence to medication; and 3) a stimulus or “cue to action” that is either internal or external to prompt the individual to adopt the advocated behavior (36). Both prospective and retrospective studies support the predictive value of the model, although results have been inconsistent, and some studies have found no association between a health beliefs score and adherence behavior (37,38).

An individual's expectations may substantially influence adherence behavior and change. Bandura described a “self-efficacy” expectation as a person's belief that he or she can successfully perform a certain behavior (29,41). A person with high self-efficacy believes that he or she is able to adhere to a certain behavior, such as remembering to take a pill as prescribed. The degree to which a person believes that he or she controls the events in his or her life may also affect adherence (29,42). Individuals who believe that, in general, their actions play a large role in determining their circumstances may tend to adhere to a prescribed treatment regimen because they believe that they can affect their own health (29). By contrast, individuals who believe that their fate is determined largely by chance and not by their own actions (29,42) may be less likely to adhere with therapy, because they feel that their actions may not appreciably affect outcomes. Depending on past successes and failures, an individual's self-efficacy expectations may be modifiable (29). These differences should be kept in mind when considering interventions to improve adherence.

Outcome expectations may also influence an individual's adherence (29,41). Although a person might believe that he is fully capable of following a prescribed treatment regimen, he may not adhere to therapy if he does not believe that his personal cost–benefit balance favors adherence. Health behaviors, including medication adherence, can be particularly hard to change because immediate consequences are generally more influential than delayed consequences. Adverse events or side effects tend to be immediate, whereas beneficial effects are generally realized only after long periods (29). Adherence is a considerable

issue with drugs that are used to treat an asymptomatic illness or to prevent illness, because there is typically an absence of immediate, apparent payoff and often the possibility of immediate adverse effects with therapy.

Although much remains to be learned about the relationship between many psychosocial characteristics and adherence, several factors appear to be important (see Table 1). These factors include the ability to follow the prescribed regimen, which is related to the complexity of the regimen, including dosing frequency; the ability to adhere to the regimen, which is related to the degree of behavioral change required and duration of therapy; convenience and efficiency of the health care setting; adequacy of supervision by and communication with health care providers; patient satisfaction; patient health beliefs, including the patient's degree of belief that the regimen will help or is worth the risks or costs; adherence history; mental illness history; family stability; and sufficiency of social support (37,38, 43-48).

One factor that has not been consistently associated with adherence is the type of disease for which a medication regimen is prescribed (with the exception of psychiatric conditions) (38). Unfortunately, rigorous data on adherence are lacking for many medical conditions, and no published studies have compared oncology patients with other patients. Demographic factors, including race, educational level, and socioeconomic status, also do not consistently appear to have much effect on adherence to therapy (38), although such factors do affect access to health care services in general. Along the same lines, there is no evidence for an association between patients' intelligence or educational achievement and adherence (38). In addition, no consistent relationship has been observed between patients' knowledge of their disease or its therapy and their adherence to the treatment regimen (37,49).

The role of age in predicting adherence is unclear. In most published studies, age is not an important predictor of medication adherence (50). Adherence among elderly patients has not been evaluated formally in oncology populations taking oral medication. However, in some studies (16,51), adherence has been found to be better in older populations than in younger ones. This difference may reflect a survivor bias to some degree, because more adherent individuals may be more likely to survive to an older age. Conversely, adherence among the elderly may be compromised by an increased number of prescribed medications for multiple comorbid conditions, by decreased social support, and by the increased incidence of memory problems in this population (50). These factors may account for the finding that very old patients may be less adherent than younger

patients (16). Adherence among adolescents has been shown to be particularly problematic (19); in several studies of adherence in various pediatric oncology populations (52-54), adolescents were the most nonadherent pediatric group.

Little information exists on the effect of the cost of therapy on adherence. In an elderly population, Col et al. (55) found an association between nonadherence and higher monthly medication costs. Other studies (56-58) have revealed marked effects of insurance coverage on adherence, particularly with regard to mental illness treatment. Chisholm et al. (59) found that renal transplant patients who received immunosuppressant therapy at no charge were generally adherent within the first year after transplantation but became less adherent over time, suggesting that drug cost alone does not explain nonadherent behavior. Furthermore, an increase in insurance copayments did not have a statistically significant effect on adherence among patients enrolled in a managed care program in one study (60); in another study (61), as charges increased, adherence actually increased in some groups, for unclear reasons. However, adherence in the latter study varied greatly depending on the drug and the socioeconomic status of the patient. Young patients, or those with poor health status, low educational level, or low income, were most likely to decrease consumption of prescription drugs when user charges increased.

The frequency, severity, and types of side effects of medications may also affect adherence, but evidence of the role of these factors is conflicting. The side-effect burden appears to affect adherence in some clinical settings but not others. Several studies (21,38,62,63), however, including those of oncology patients, have found no relationship between side effects and adherence. It is likely that side effects, like many other factors, are only one piece of a complicated puzzle.

Finally, the relationship between the patient and his or her health care practitioners may affect adherence (64-66). Specific physician practices and continuity of care may be important (38), along with the convenience of the clinic, including location and open hours and ease of scheduling. Long waiting times before and during appointments with their physicians are major reasons patients give for failure to keep subsequent appointments, and these factors are also likely to affect adherence to medications (38).

MEASURING ADHERENCE

An important problem in assessing adherence is the lack of a gold-standard measurement (67). Many methods have been used to measure adherence, each of which is limited by biases and methodologic flaws (68). The potential effect of the measurement itself, termed the "Hawthorne effect," must be considered (63,69,70). This is the effect (often beneficial or positive) of observation itself on the outcome (70,71). Frequently, an individual's knowledge that he or she is under study influences behavior and may therefore affect adherence. This is not generally a problem in the treatment of patients outside a research setting, because the primary goal of monitoring adherence in this setting is to improve adherence among individuals. In the research setting, where adherence may be monitored for only a representative subset of the patients, it is generally more important to have an accurate measure of adherence so that the true effect of any experimental therapy can be assessed.

Continuous dose observation is the most precise way to monitor adherence, but this method is both impractical and highly

Table 1. Factors often associated with nonadherence to prescribed oral medication regimens*

Complex treatment regimen
Substantial behavioral change required
Inconvenient or inefficient clinics
Inadequate supervision
Poor communication with health care providers
Patient dissatisfaction with care
Patient health beliefs in favor of nonadherence
Inadequate social support
History of nonadherence
History of mental illness

*Ref. (37,38,43-48)

prone to the Hawthorne effect. Traditionally, self-reporting has been used to measure patient adherence to oral therapies. However, patient recall is frequently inaccurate and biased by a patient's reluctance to admit "bad" behavior to the health care team. Thus, self-reporting has been criticized as too subjective, with a tendency for patients to over-report adherence to therapy (72). Some studies (73,74) have, not surprisingly, shown that self-reporting tends to be accurate for patients who admit that they are not taking their prescriptions, although more recent data (Wang PS, Benner JS, Glynn RJ, Winkelmayr WC, Mogun H, Avorn J: manuscript in preparation) suggest that adherent patients sometimes report nonadherence. Pill counts, another method to evaluate adherence, can also be unreliable (75,76), because patients can manipulate them, particularly when they know that their pills will be counted. Furthermore, pill counts provide no information about adherence to dosing schedule. In addition, several studies (13,77) have shown that, as adherence declines, pill counts become even less accurate for measuring adherence.

Drug or metabolite levels in serum or urine provide more objective measures of adherence than patient self-report, but such levels may vary widely because of individual pharmacokinetics (i.e., rates of absorption, distribution, metabolism, and excretion). In addition, patients who are nonadherent may take additional doses just before a physician visit, and their drug levels may, therefore, falsely suggest good adherence (78). Measurement of surrogate markers or biologic endpoints of drug therapy [e.g., estrogen levels in patients taking estrogen-lowering drugs or serum dehydroepiandrosterone sulfate suppression in patients on steroids (79)] is another way in which researchers can assess adherence, although the costs of such tests may be prohibitive for routine use outside a research setting. Furthermore, if a therapy is not efficacious in a given individual for biologic reasons, such as resistant disease, biologic endpoints may not reflect adherence rates.

The microelectronic monitoring system (MEMS) is a newer method to assess adherence. The system entails the use of an "intelligent" tablet bottle that electronically records the time (to the nearest hour) and date when the cap is removed. The data are collected for up to several weeks and are recorded and processed by a computer to generate a list of the dates and times of bottle openings, a graphic representation of the number of doses taken daily, the number of missed or extra doses, and the dosing intervals (13,63,80,81). Problems with this method include the expense and impracticality of large-scale monitoring of patient populations, both within a clinical trial and outside the research setting. Furthermore, receiving a different bottle from the usual may itself influence adherence. Because patients must consent to be included in studies using MEMS, their awareness of being part of a study may also influence adherence (80). In addition, being asked to bring pill bottles to each clinic visit may affect a patient's adherence. Finally, the act of opening a pill container does not necessarily mean that the patient ultimately ingested the pill as prescribed.

Pharmacy and insurance records can be used to assess adherence in large populations over extended periods of time (74). Analyzing records of prescriptions actually filled makes it possible to use standardized data from a pharmacy or large insurance database to define continuity of medication use and gaps in therapy. Patterns of ongoing prescription filling probably provide the most accurate estimate of actual medication use in large

populations (14). One widely used approach is the "days-covered" method, in which the total number of doses available to a subject for a given period (as evidenced by refill rates and size of refills) is divided by the number of doses that would be necessary for that same period to achieve 100% adherence with the prescribed regimen. However, this method provides no information about how a patient is taking the medication (e.g., dosing interval). In addition, although most people probably do not bother refilling prescriptions that they are not taking, prescription refills do not absolutely translate to a patient's consumption of the drug.

Another important advantage of assessing adherence using large databases, including those from Medicaid, Medicare, and health maintenance organizations, is the ability to document all health care services used, including prescriptions, without recall bias or incomplete history information. However, the limitations of this claims-based information must also be considered (82). These databases are often composed of specific patient populations (e.g., the elderly or the poor) and, thus, findings from such studies may have limited generalizability. In addition, individuals may discontinue their use of drugs on the advice of their doctors because of side effects or lack of effectiveness, reasons that may not be apparent from available database information (16). It is not clear that discontinuation for such reasons should be considered nonadherence in the conventional sense. No published oncologic studies have used analysis of large databases to assess adherence. For anticancer drug regimens that are prescribed for long periods, such as adjuvant tamoxifen, this method may be ideal for assessing overall adherence in large populations. However, in general, when using medication adherence as an outcome measure or a modifying variable, investigators should be aware of the limitations of the methodologies used and interpret their results with caution (83).

STUDIES OF ADHERENCE TO ORAL CHEMOTHERAPY

Relatively few published studies on adherence have focused on adherence to oral chemotherapy, in part because the vast majority of chemotherapy has been delivered intravenously in physicians' offices or hospitals. Clinical trials in oncology have generally assessed adherence to oral agents via pill counts and patient self-reporting, both of which are fraught with the methodologic problems outlined above. Metabolite levels in serum or urine have also been used when feasible. In clinical trials, reported adherence to oral agents such as adjuvant tamoxifen has ranged from 72% to 96%, but the assessment methodology has generally not been described (84–88). Furthermore, patients participating in clinical trials are generally highly motivated to adhere to treatment and are closely monitored (89). Therefore, their adherence rates may not accurately reflect patient behavior in the general oncologic population.

We designed a search strategy to identify studies that examined adherence to oral antineoplastic agents among oncology patients. A MEDLINE® search for English-language articles published from 1980 through 2001 was performed, linking the subject search headings "compliance," "adherence," and "persistence" with each of the following headings: "chemotherapy," "oral therapy," and "antineoplastic agents." We restricted our review of studies of oral anticancer therapy to those in which adherence was a primary outcome and for which the method of adherence measurement was defined explicitly. Manual searching of the reference lists within relevant articles identified ad-

ditional studies. We identified six studies in adults (Table 2) and six in pediatric populations (Table 3). Because of the diverse nature of the study designs, a quantitative synthesis is not possible; instead, we discuss some of the issues the studies raise.

The few studies that have focused specifically on adherence to oral antineoplastic agents in adults have yielded variable results (Table 2). In the largest published study of adherence in adult oncology patients, Levine et al. (72) followed 108 patients with newly diagnosed hematologic malignancies and assessed adherence to oral self-administered daily allopurinol and intermittent prednisone, and to monthly scheduled appointments. Metabolite levels in serum, assessed monthly over 6 months, were used as indicators of adherence to the drugs; when patients had metabolite levels above a certain expected threshold, they were considered adherent. Patients were fully adherent to allopurinol an average of only 16.8% of the time—that is, 16.8% of

times measured, patients had at least the minimal level of serum allopurinol metabolites. Adherence increased to 44%–48% of the time on average for patients who received any one of three intervention programs: education, home psychological support and restructuring, and training in pill-taking, including practicing self-medication in a controlled environment. Patients were fully adherent to prednisone only 26.8% of the time, and intervention did not lead to substantial improvement in this adherence rate.

Although this study used serum levels of drug metabolites to assess adherence, patients were also asked to self-report adherence. The self-reports overestimated adherence by a factor of two (72). The occurrence, frequency, and severity of side effects did not predict nonadherence to either medication (62). However, these factors did predict nonadherence to clinic appointments to receive infused chemotherapy (62,72). This study

Table 2. Published studies of adherence to oral antineoplastic agents in adult populations

Cancer in study population	No. of subjects	Oral therapy	Adherence measure	Adherence rate	Ref.
Hematologic malignancies	108	Prednisone Allopurinol	Serum prednisone and allopurinol metabolites	Prednisone, 26.8% Allopurinol, 16.8%	(72) (62)
Breast cancer	51	Oral cyclophosphamide and/or prednisone	Patient self-report (dosage adherence: ingesting more than 90% of sum total prescribed = adherence; behavioral adherence: ingesting more than 90% and less than 110% of drugs prescribed reported at each visit)	53% overall adherence with both drugs	(21)
Hodgkin's disease or non-Hodgkin's lymphoma	21	Chlorambucil, prednisolone, or dexamethasone	MEMS*	100% (SD ± 20.6%)	(63)
Small cell lung cancer	12	Etoposide	MEMS	93.2% (SD ± 12%)	(80)
Breast cancer	26	Tamoxifen	Self-report Pill count MEMS	97.9% (SD ± 3.0%) using self-report 92.1% (SD ± 9.8%) using pill counts 85.4% (SD ± 17.2%) using MEMS	(13)
Ovarian cancer	11	Altretamine	MEMS	97.4% (SD ± 6.9%)	(89)

*MEMS = microelectronic monitoring system; SD = standard deviation.

Table 3. Published studies of adherence to oral antineoplastic agents in pediatric populations

Cancer in study population	No. of subjects	Oral therapy	Adherence measure	Nonadherence rate	Ref.
Leukemia or non-Hodgkin's lymphoma	52	Prednisone	Threshold urinary prednisone metabolites assay	33% of children overall did not meet expected levels (59% in adolescent subgroup)	(52)
Acute lymphocytic leukemia (ALL)	31	Prednisone	Threshold urinary prednisone metabolites assay	42% of children had average assays below threshold	(91)
ALL	327	Maintenance therapy with 6-mercaptopurine (6-mp)	Two 6-mp metabolites in red blood cells	10% had both levels in lowest quartile, 3% had one or both levels absent	(92)
ALL	496	Maintenance therapy with 6-mp	Two 6-mp metabolites in red blood cells	2% had absent levels of metabolites	(54)
Leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, other malignancies	46	Combinations of prednisone, 6-mp, methotrexate, procarbazine, and tamoxifen	Self report and parent report (nonadherer if more than one missed dose/month) Serum bioassay for prednisone (bioassays corroborated data from patient report)	At 50 weeks, 65% adherent, 25% occasional missed doses, 10% frequent missed doses	(53)
ALL, Hodgkin's disease	50	Prednisone or prophylactic penicillin	Serum dehydroepiandrosterone sulfate suppression and urinary growth inhibition assay (for penicillin)	52% of those taking prednisone (11/21) were nonadherent, 48% of those taking penicillin (14/29) were nonadherent	(79,93)

raises the question of whether decreased adherence to oral chemotherapy, particularly for highly chemosensitive malignancies, might translate into negative outcomes. On a positive note, the results suggest that interventions can result in some improvement in adherence.

Another study of adherence was conducted by Lebovits et al. (21) on 51 breast cancer patients enrolled in protocols that included orally administered cyclophosphamide and/or prednisone. The investigators determined patient-reported adherence for four 1-week intervals, at the end of weeks 2, 4, 13, and 26, on therapy. They used two summary measures of nonadherence: dosage and behavior. Dosage was defined as the overall percentage of drug missed during each week-long assessment period, with nonadherence defined as a patient reporting ingestion of 90% or less of the total prescribed dose of either prednisone or cyclophosphamide, summed over all four self-report intervals. Behavioral nonadherence was defined as a patient reporting taking 90% or less or 110% or more of either cyclophosphamide or prednisone at any one of four patient visits. Twenty-four patients (47%) met criteria for nonadherence to cyclophosphamide according to at least one of the definitions, and 22 (43%) met these criteria with regard to nonadherence to prednisone. Twenty-two patients (43%) met criteria for nonadherence according to both definitions, and only two patients met only behavioral nonadherence criteria.

Evaluation of the type of nonadherence among the 22 patients who were nonadherent (according to both definitions) showed that 12 patients had over-ingested one or both drugs, eight had under-ingested the drugs, two had both over- and under-ingested the drugs, and two had elected to discontinue chemotherapy. Patients taking both drugs were more likely to be nonadherent than were patients on single-drug therapy. For both drugs, patients were more likely to remain on the prescribed schedule earlier in the course of therapy than later. Physical symptoms, demographics, and psychological characteristics were not associated with patient nonadherence on multivariable analysis. One factor that did appear to affect adherence was treatment location; adherence was poorer in community and clinic settings than in an academic setting (21). Patients with lower incomes were also less adherent (21). The potential dangers and toxicities of over-adherence, as seen in this study, are of concern when administering oral chemotherapy.

In several studies (13,63,80,81), oral antineoplastic therapy has been associated with higher rates of adherence when measured with the MEMS device (see Table 1). In three small observational studies by Lee and colleagues (63,80,81), no substantial differences in adherence rates as measured with MEMS were found in groups with different diseases of varying severity. Regimen, side effects, and quality of life were not consistently associated with adherence rates in these studies. In a study of 26 patients with breast cancer, Waterhouse et al. (13) found that patient self-reports and pill counts statistically significantly overestimated the degree to which patients adhered to their tamoxifen regimen, as compared with data recorded by the MEMS device. In this study (13), patients were monitored for approximately 3 months and classified as adherent if 80% or more of the tamoxifen doses were taken as prescribed. This rate was chosen as the cutoff because it is frequently cited in the literature as achievable or acceptable (13,82,90). When all dosing errors as measured with MEMS were considered, 18 of 24 patients were nonadherent, that is, they took less than 80% of

their doses as prescribed (including dose omissions and/or schedule errors) during the monitoring period. If only dose omissions as recorded with MEMS were considered, patient adherence rates ranged from 36.4% to 100%, with an overall average of 85.4% (standard deviation \pm 17.2%).

Although patients were not informed before entry into this study that their adherence was to be monitored electronically via MEMS, they were asked to open the container only if they intended to take the drug. Furthermore, patients were informed that they would be asked to complete questionnaires concerning their pill-taking habits. They were also asked to bring their tamoxifen bottle to the clinic at each visit, so that their physician "could assure that they were receiving the proper medication in the correct dose" (13). Thus, even in this setting, in which patients were most likely aware of some monitoring of drug adherence, patients were not fully adherent. It is noteworthy that tamoxifen is one of the least toxic and best tolerated of the effective oral treatments available in oncology.

CHILDREN AND ADOLESCENTS

The findings from adherence studies in pediatric oncology populations (Table 3) reveal that a substantial proportion of children are minimally adherent. Nonadherence rates appear to be highest in adolescents (19,52–54).

In one study of adherence in pediatric patients, Smith et al. (52) used a urine assay for a 17-ketogenic steroid drug metabolite to differentiate between patients who were taking prednisone as directed and those who were not. In 52 pediatric patients with leukemia or non-Hodgkin's lymphoma, 33% of children overall and 59% of the adolescents were poorly adherent, as defined by lower-than-expected levels of the urinary prednisone metabolite when sampled at random times.

Using the same assay to measure adherence to oral prednisone in 31 children with acute lymphocytic leukemia (ALL) who were younger than 15 years, Lansky et al. (91) found that no patients were completely adherent. All children had at least one of three urinary assay values less than a threshold level indicative of adequate adherence with oral prednisone. Moreover, only 18 of the children (58%) had average assay values "at the threshold or above," consistent with overall "adequate" adherence. However, the range of assay values varied widely within and among children. As the authors point out, this variation exemplifies the continuum of adherence, with some children taking little or no prednisone, some taking most or all of their pills, and the rest adhering sporadically or partially (91). Although adherence rates were the same for girls and boys, the psychological characteristics of the girls who were more adherent, compared with the boys, and those of their parents, as measured by standardized tests, were quite different. Certain parental personality traits and attitudes, including hostility, anxiety, and obsessive-compulsive behavior, were more often associated with adequate adherence among boys than girls. Among the girls, higher individual levels of anxiety were associated with better adherence.

In another study, Lennard et al. (92) assessed adherence to oral 6-mercaptopurine by measuring levels of two metabolites in red blood cells in 327 children on maintenance therapy for ALL. Each child had been prescribed the same protocol-directed dose for a minimum of 7 days before the assay. The concentrations of the metabolites varied widely among the children. No child had both metabolite concentrations in the upper two quartiles, and for 32 children (10% of the total), the concentration of both

metabolites was in the lower quartile. Among these 32 patients, only one metabolite could be detected in four children, and neither metabolite was detected in six children. This study reveals that a substantial minority of children with ALL fail, totally or intermittently, to take their oral 6-mercaptopurine. In a similar population of 496 children, Lancaster et al. (54) found that nine children (2% of the total) had undetectable levels of 6-mercaptopurine metabolites. Five of the nine children were adolescents—more than would be expected by chance—and most of this highly nonadherent group had been receiving treatment for more than 1 year. No other predictor was associated with nonadherence.

Confirming the problem of nonadherence in adolescent populations, Festa et al. (79) assessed outpatient adherence to prednisone or prophylactic penicillin in 50 adolescents in remission from ALL or Hodgkin's disease. Of the 21 patients taking prednisone, 11 (52%) were nonadherent as determined by the absence of a suppression of dehydroepiandrosterone sulfate (DHEA-S) levels, as would have been expected if they were taking their prednisone as directed. Of the 29 patients who were prescribed penicillin, 14 (48%) were nonadherent as determined by a lack of urinary penicillin detected by bioassay. Individual adherence status did not change at follow-up (i.e., after 3–6 months). Although treatment or sociodemographic variables of adherent patients did not differ statistically significantly from those of nonadherent patients, certain psychological characteristics did predict nonadherence among 34 patients who were assessed as part of this study (93). Nonadherers had a less well developed understanding of their illness, including causality and prognosis; less perceived vulnerability (especially when asymptomatic); less coherent future orientation (i.e., less integration of events as they unfold with time); and higher levels of denial. These results, in accordance with a biopsychosocial model of adherence, suggest that adherence in adolescents may be affected by an individual's subjective assessment of his or her illness and its treatment.

The true extent of the problem of nonadherence among pediatric oncology patients is unknown. Furthermore, the relationship between parental involvement and adherence is probably very important and has not been well studied. Nonadherence is clearly clinically important, at least in patients with ALL, because children with lower concentrations of 6-mercaptopurine metabolites in their red blood cells are at higher risk of relapse (94,95).

ADHERENCE ISSUES IN CANCER PREVENTION

Adherence may vary depending on whether an individual has overt disease or is simply at risk for a given disease (5). The long duration of prevention trials and the absence of overt disease may decrease adherence to preventive interventions. Being at high risk for a disease such as cancer may be a powerful stimulus for adherence; however, the data are inconclusive for regimens that need to be taken over a prolonged period (96).

Adherence figures from the Physicians' Health Study were relatively high: among the 22 071 male physicians randomly assigned to receive either beta-carotene or placebo, fewer than 1% had been lost to follow-up after 12 years, and 80% of the men that received beta-carotene reported remaining on the drug, with an average self-reported compliance (taking the pill daily) of 97% in this group (97). However, in another long-term chemoprevention study of beta-carotene and alpha-tocopherol (98–

100), nonadherence, as measured by dropout rate, was much higher, with 25% of the participants dropping out of active follow-up before the scheduled end of the study. Similarly, in a skin cancer chemoprevention trial (101), in which 2297 participants were randomly assigned to receive 25 000 IU of retinol or a placebo daily for a median follow-up time of approximately 4 years, 677 (29.5%) of the participants dropped out during the 5-year study.

When evaluated in the prevention setting, predictors of nonadherence are few. In the previously described skin cancer prevention study (6), the only statistically significant predictors of dropout were low educational level (hazard ratio = 1.6, 95% CI = 1.2 to 2.2) and being unmarried (hazard ratio = 1.3, 95% CI = 1.1 to 1.6). There was no statistically significant difference in the number of participants who dropped out by treatment group, sex, prior health status, vitamin or sunscreen use, smoking history, or employment status. The most common reasons for dropping out were illness of the subject, a spouse, or a close relative (18.6% of those who dropped out) and experiencing an undesirable clinical symptom consistent with vitamin A ingestion (17.1%). The dropout rate was highest in the first month of the trial and declined thereafter. This latter finding and data from other studies provide evidence that interventions such as a run-in period before a trial, during which potential subjects are selected on the basis of their adequate adherence (usually to a placebo), may be effective in reducing dropout in the actual trial and thereby increasing adherence in chemoprevention trials (102). This approach could possibly limit the generalizability of the trial results to a nonclinical trial patient population in which nonadherence may become a larger issue.

Adherence to chemopreventive drugs has become an important issue in breast cancer prevention, now that the Food and Drug Administration has approved tamoxifen to lower breast cancer risk (103,104). Veronesi et al. (88) compared adherence among women on trials who were receiving tamoxifen as adjuvant therapy after surgery only with those who were prescribed tamoxifen for chemoprevention as part of the Italian Tamoxifen Prevention Study. Patients treated within the adjuvant studies reported more adverse effects, including hot flashes, vaginal discharge and/or bleeding, and weight gain, than those treated in the chemoprevention study. However, permanent discontinuation reportedly occurred in 15.1% of patients in the adjuvant studies and 26.7% of patients in the chemoprevention study—a statistically significant difference. The preliminary report of the Royal Marsden Tamoxifen Prevention Programme study (105), another randomized, placebo-controlled study of tamoxifen for breast cancer prevention, showed that 70% of women receiving tamoxifen remained on study at 5 years, compared with 80% of women receiving placebo. These data suggest that the side effects that an individual experiences may have a more substantial effect on adherence in the prevention setting, when a patient is only at risk for a disease rather than having overt disease.

To date, no information is available on the use of tamoxifen or other chemopreventive agents outside a clinical trial. Future studies focusing on this aspect of cancer prevention are warranted and may reveal that adherence outside the research setting is dramatically worse than adherence during a trial.

CONCLUSIONS

Oral chemotherapy can be effective only if adherence is optimized. The limited evidence that is available suggests that

nonadherence may have a substantial impact on the therapeutic success or failure of oral regimens for the prevention or treatment of malignancies. Adherence should never be assumed, even in oncology; every patient is at risk for nonadherence (106,107). A constellation of factors are associated with nonadherence, including characteristics of the treatment regimen, the patient, the patient's social environment, and the clinician-patient interaction. Patient perceptions and motivations appear to be the most important determinants of adherence. Knowledge of the factors associated with nonadherence can alert clinicians to situations in which adherence is likely to be suboptimal and help them target interventions to areas that may be amenable to change.

Few studies have evaluated "real-life" (i.e., outside a research setting) adherence issues surrounding the administration of oral chemotherapeutic agents (108). These issues should be studied further with a theoretical model that incorporates a range of biopsychosocial variables to determine risk factors for nonadherence among oncology patients. Although few interventions targeted at biopsychosocial factors have been studied, some may improve adherence among cancer patients (72,109). Interventions that have produced some improvement in adherence among oncologic populations are few and include educational programs; behavioral modification techniques, such as practicing pill-taking; and use of reminder systems and cues (7). At a minimum, clinicians should consider asking patients if they are taking their medication(s) as directed, what they expect or are experiencing from the medication(s), and whether they are having problems with adherence. Such affective interventions, along with other low-tech aids, such as daily pill boxes, are relatively inexpensive and have been shown to improve adherence in other patient populations (109).

Future research should also consider the costs and benefits of monitoring adherence in routine patient care and of implementing interventions to improve adherence. In addition, the degree of nonadherence that can be tolerated without compromising outcomes and the amount of improvement in adherence and outcomes following potential interventions are not clear. Efforts to systematically assess and ensure adherence should be built into oncology patient care—particularly for phase III studies and off-study treatment with oral antineoplastic agents—to ensure that current and future patients receive the full benefits of their treatments.

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NOTE

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