

# Adherence to oral antineoplastic agents by cancer patients: definition and literature review

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## Adherence to oral antineoplastic agents by cancer patients: definition and literature review

Since the 1990s, oral chemotherapy has been gaining ground as cancer treatment. This therapy seems to have few toxic effects and offers patients good quality of life. However, in addition to the fears the therapy might generate in patients, oral treatment raises a new issue, which, until now, has been marginal in this field: therapeutic observance or adherence. We investigated the research into adherence to oral chemotherapy among cancer patients published between 1990 and July 2013. Studies showed considerable diversity in terms of both the definition and measurement of adherence. As well, adherence to antineoplastic therapy is affected by the patient's understanding of the treatment and ability to remember information provided by the physician, treatment length and psychological distress. Our review of the few studies on adherence to anticancer drug treatment raises some questions that could be pursued in future research. In light of our findings, patients should receive 'therapy education' to help them and their support groups better understand the disease and its treatment and to achieve optimal health management and improved treatment effectiveness.

*Keywords:* cancer, oncology, adherence, compliance, treatment, oral chemotherapy, systematic review.

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## INTRODUCTION

In oncology, unlike most biomedical disciplines, medication as chemotherapy is mainly administered intravenously (O'Neill & Twelves 2002; Campone *et al.* 2007; Palmieri & Barton 2007; Findlay *et al.* 2008; Khandelwal *et al.* 2012). However, since the 1990s, oral chemotherapy has been gaining ground. Today, 20% to 25% of all drugs

used in cytotoxic chemotherapy, called antineoplastic agents, can be administered orally (Bedell 2003; Findlay *et al.* 2008) and this proportion is increasing. Today, more than half of the new drugs developed are taken orally (Given *et al.* 2011). However, this therapeutic trend has had a number of consequences for patients, who are now playing a more central role in their healthcare, still uncommon in this type of disease (Accordino & Hershman 2013). One issue with oral chemotherapy is patient adherence to treatment.

Among the main advantages of oral cancer treatment, the advantages most often cited are no need to enter veins (Cassidy 2005), the low frequency of hospitalisation (Faithfull & Deery 2004) and the reduced time needed for caregiving staff (Findlay *et al.* 2008), not to mention the small number of undesirable effects (although toxicity profiles vary by molecules). Despite few studies in this area, patients overwhelmingly prefer oral over intravenous administration (O'Neill & Twelves 2002; Catania *et al.* 2005; Aisner 2007), with proportions from 53% (Institut Européen du Cancer 2005) to 89% (Liu *et al.* 1997) favouring oral therapy. In one study, after treatment by both routes, 57% of patients preferred the oral route (Pfeiffer *et al.* 2006). Patients most often fear that this type of chemotherapy is less effective, although 40% consider that oral chemotherapy is less toxic (Palmieri & Barton 2007) and offers better quality of life (Campane *et al.* 2007) and is an easier method of administration (O'Neill & Twelves 2002) than intravenous therapy. Finally, oral treatment is associated with a feeling of freedom (Catania *et al.* 2005) and a strong sense of control over one's treatment and the evolution of the disease (Liu *et al.* 1997).

However, the novelty of oral chemotherapy for cancer has also elicited ambivalent attitudes and beliefs. The change to oral administration is sometimes seen as a last attempt before entry into the palliative phase, although this is not always the case (Regnier-Denois *et al.* 2011). Indeed, the therapy can be implemented to decrease discomfort for patients, intravenous chemotherapy being too difficult to implement. Patients may feel that they are abandoned by medical staff, a feeling also experienced during a remission phase (Catania *et al.* 2005). Patients may also feel that they are being used as 'guinea pigs' for experimentation with new drugs (Regnier-Denois *et al.* 2009). Finally, oral medication may suggest that the disease has become chronic, as in diabetes (Regnier-Denois *et al.* 2009).

The term 'adherence', used by most authors as synonymous with 'observance' and 'compliance', is not limited solely to the administration of medication. It also encompasses behaviours such as keeping appointments at the

hospital or physician's office, eating a healthy balanced diet, doing physical exercise and refraining from smoking, etc. (Tarquinio *et al.* 2000). Haynes defined adherence as 'the extent to which a person's behaviour (in terms of taking medication, following diets or executing other lifestyle changes) coincides with medical or health advice' (Haynes *et al.* 1979). Osterberg and Blaschke (2005) recently defined adherence as 'the extent to which patients take medications as prescribed by their health care providers'. In a narrower sense, adherence refers to taking medication as prescribed and/or agreed upon by the patient and the healthcare professional (Cramer 2004). According to Haynes' definition, the patient is placed in a manifestly passive position: the physician's prescriptions and directions define the framework of adherence. Yet the situation, type of disease, and patients' understanding and acceptance of what they are experiencing will also influence adherence behaviour. As a result, non-adherence cannot be reduced to a patient's non-compliance with the expectations of physicians and other healthcare professionals.

Medication adherence can be measured in two ways (Blackwell 1973, 1992; Morisky *et al.* 1986; O'Brien *et al.* 1992): direct and indirect. Direct measures are obtained from the patient's biological markers, indicators of the stage or evolution of the disease that signal whether and to what extent the patient has taken the prescribed medicine. Direct measures can be also obtained by detecting the presence of the prescribed substances in blood or urine. These measures provide information about the patient's behaviour. Such 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 visit to the doctor, so testing methods would not take into account a patient's intermittent use of medication. These methods may also complicate the physician-patient relationship because patients may perceive that these methods indicate lack of trust by their care provider.

Indirect measures, such as patient self-reported data, considered less 'objective' than direct measures (Myers & Midence 1998), appear to be easier for practitioners and clinicians to obtain (Besch 1995). Caron (1985) noted that indirect measures were used alone or in combination in more than 68% of studies conducted between 1977 and 1983. Among the methods used to obtain indirect measures, the most prevalent were questionnaires (self-administered or not) and semi-structured interviews (Haynes *et al.* 1979; Kass *et al.* 1984, 1986). 'Self-reporting' refers to measures provided by patients themselves, to distinguish them from assessments made by medical team

members asked to give their opinions about patients' adherence behaviour. Patient self-reports and diaries can be used, but patients may overestimate their adherence to please their physicians. In clinical trials, various counting techniques are used to obtain indirect measures. Adherence in this case is measured as the difference between the number of pills prescribed and the number remaining in the dispenser, which is equipped with a sophisticated electronic counting device (Bond & Hussar 1991). Some highly accurate measuring systems have been developed, such as the original one by Kass [Medication Event Monitoring System (MEMS); Kass *et al.* 1984 1986]. A pill-box monitor can be used to store the number of times the box is opened to take out a pill and how long the box stays open (Geletko *et al.* 1996).

The first studies on medication adherence, which date back to the 1970s, showed that 50% of hypertension patients did not fully comply with medical prescriptions (Cotton & Antill 1984). Later, more than 80% of patients with chronic diseases such as diabetes (Kravitz *et al.* 1993), asthma (Bailey *et al.* 1990; Brooks *et al.* 1996) or hypertension (Hamilton *et al.* 1993) were found not to properly follow their treatment regime (i.e. not well enough to attain optimal therapeutic benefits). According to Myers and Midence (1998), non-adherence extends the duration of a disease (from 10% to 20% of cases in their study), contributes to increased sick leave from work for health reasons (from 5% to 10% of cases), increases the frequency of visits to the general practitioner or specialist (from 5% to 10% of cases), and lengthens hospitalisation time (by 1–3 days, on average). Likewise, Gryfe and Gryfe (1984) found that 15% of hospitalisations of older adults were due to poor medicine-taking behaviour.

Of note, consensus is lacking on a cut-off that defines adherence or non-adherence (Ankri *et al.* 1995). For Gordis *et al.* (1969), patients are not considered to have proper adherence to penicillin-taking unless urine analyses indicate 75% presence of the active ingredient. For Ebrahim (1998), patients are considered to adhere to treatment when they take more than 80% of the pills prescribed for high blood pressure and also attend appointments. Finally, Paterson *et al.* (2000) contend that a minimum of 95% adherence is necessary to obtain optimal prevention of virus replication in HIV-AIDS.

This general presentation of the problem of adherence and its assessment can help illuminate the introduction of oral treatment with antineoplastic agents in the specific case of cancer. Here we performed a literature review to assess adherence with oral therapy for cancer.

## METHODS

### Literature sources and search terms

Two teams of three experts each performed an independent search of the literature to identify articles of research into oral treatment adherence in adult patients with cancer in the following electronic databases: FRANCIS, PubMed and PsycInfo. We used the terms cancer, oral chemotherapy, oral agents, oral antineoplastic agents/treatments, observance, adherence and compliance to search for articles of studies of oral anticancer therapy in which adherence was a primary outcome and for which the method of measuring adherence was explicitly defined. We limited the search to articles published in English and French between January 1990 and July 2013.

Studies had to involve two chemotherapy agent categories: cytotoxic agents and targeted therapy (such as monoclonal antibodies and kinase-tyrosine inhibitors). We did not include articles about corticoids, hormone-dependant therapy or biological response modifiers (cytokines and immunotherapeutic agents). We excluded studies of treatments to relieve symptoms (e.g. analgesics). Our review differs from that of Partridge *et al.* (2002), which also concerned hormone-dependant therapy and corticoids not used as chemotherapy.

We also searched the reference lists of relevant articles to identify other articles. We downloaded the articles to an online research management tool and removed duplicates.

### Inclusion criteria for articles

The initial search resulted in 518 articles. After reading the abstracts for any mention of measuring adherence to oral antineoplastic therapy, we retrieved the full text for 62 articles. The two research teams reviewed the full text of each article independently of one another to determine eligibility, then compared results and came to an agreement about which articles to include and exclude. A total of 21 articles were included in the study.

We extracted the following data from each article: first author name and year of publication; country where the study was conducted; type of cancer and/or affected organ as well as disease stage; treatment administered; definition of cut-off for adherence; characteristics of the sample (number of men and women, mean age); method(s) used to assess adherence (direct or indirect measures) and details of each method; time when adherence was assessed; adherence results (adherence rate according to assessment method, factors associated with adherence); and conclusions.

## RESULTS

The main characteristics of the 21 articles dealing with adherence to oral antineoplastic therapy among cancer patients are summarised in Table 1. The studies were diverse in types of cancer, populations studied and stages of the disease. In all, 14 articles described patients with solid tumours, six articles malignant haemopathic conditions and only 1 article both population types. In addition, the differing sample sizes (range 11–516) did not afford the same generalisation for all outcomes.

In seven articles, adherence was considered to occur only when it was perfect (i.e. 100% of the prescribed medication taken). The lowest rate established for adherence was 80% (Mayer *et al.* 2009), which the authors deemed 'acceptable'. Some studies did not mention a cut-off (Lee *et al.* 1992; Sommers *et al.* 2012), but others categorised adherence from very high (95% to 100%) to low (0% to 50%) (Darkow *et al.* 2007; Gebbia *et al.* 2013).

Studies greatly differed in adherence-measuring methods: six articles described several measures; eight, a MEMS; two, direct biological tests (urine tests); three, interviews; and four, questionnaires or a diary. Pill counting was infrequent: only four articles described this method.

Adherence was most often measured from 6 to 10 weeks, with two studies measuring for as long as 9 months (Noens *et al.* 2009) or 12 months (Darkow *et al.* 2007); two others proposed follow-up for several years, from 3 years (Moon *et al.* 2012) to 39 months (Ganesan *et al.* 2011).

Adherence was evaluated at study inclusion, at the end of treatment, or on each treatment/appointment cycle, which suggests that measurement time is an important factor in assessing therapeutic adherence. Gebbia *et al.* (2013) did not give a temporal limit but stated that adherence evaluation was monthly. One study measured adherence once during treatment (Sommers *et al.* 2012).

The adherence rates ranged from 40% (Uematsu *et al.* 1996) to 100% (Lee *et al.* 1992). These rates are relatively good as a whole, given the well-known reference of 85% generally deemed acceptable. Adherence rates in studies with low to intermediate adherence ranged from 40% (Uematsu *et al.* 1996) to 78% (Gebbia *et al.* 2013). In the Decker *et al.* (2009) study, one patient in four did not adhere to a Xeloda or Tyverb treatment schedule [among the 'targeted chemotherapies', le Tverb (lapatinib) is indicated for some metastatic breast cancer]. With Glivec, one patient in five received half of the treatment (Darkow *et al.* 2007) and 30% of patients interrupted their treatment for at least 1 week (Ganesan *et al.* 2011). The two most widely affected adherence factors were number of

intakes and time between intakes. In one study, only 43% of the patients took the proper amount of medication (Lebovits *et al.* 1990) and in another, 45% did not comply with the prescribed time lapse between intakes (Klein *et al.* 2006). Adherence also decreased over time. For example, the adherence rate for Xeloda was 87% for cycle 1 but dropped to 78% for cycle 2 (MacIntosh *et al.* 2007). In the Khandelwal *et al.* (2012) study, the adherence was from 99% at 1 month to 64% at 3 months and 43% at 6 months. Among the most frequent intake errors was over-adherence, which ranged from 20% (Spoelstra *et al.* 2013) to 44% (Mayer *et al.* 2009). Completely stopping treatment was rare, with a rate of 4% in the Lebovits *et al.* (1990) study. Finally, we have little information about the long-term effect of chemotherapy used for chronic conditions, such as chronic leukaemia. Indeed, Moon *et al.* (2012) showed that 92% of patients always take Glivec after 3 years of treatment.

Determinants of adherence were numerous and heterogeneous; we identified poor sleeping, long duration of treatment, side-effects, and high number of drugs taken as determinants of poor adherence. However, five studies did not explore determinants of adherence (Uematsu *et al.* 1996; Sadahiro *et al.* 2000; MacIntosh *et al.* 2007; Mayer *et al.* 2009; Moon *et al.* 2012).

## DISCUSSION

The problem of adherence to therapy is not new to oncology. However, the arrival of oral treatment for cancer more than simply grants a central role to the patient: it actually redefines that role and the patient's commitment to therapy. This situation is comparable to that of patients with a chronic disease, for which self-managing treatment necessarily requires autonomy and self-reliance. Until now, cancer patients were given chemotherapy at the hospital, but today's advances in cancer research have allowed for oral antineoplastic therapy at home.

A patient's understanding and retention of treatment information has long been considered a factor likely to influence adherence behaviour. Patients must acquire new knowledge to manage oral chemotherapy on their own outside of the secure and supportive environment provided by the hospital. They must understand and remember the many ways of taking their medication, instructions to be followed, and rules of daily hygiene to adopt. Some examples are intake schedules (e.g. 30 min after a meal for Xeloda, standardisation of daily hours for Afinitor, intake before eating each morning for Endoxan), intake modes (with a liquid, after washing hands), possible treatment interruptions (period without taking Xeloda or

**Table 1.** Characteristics of the 21 studies conducted on the topic of treating cancer with oral chemotherapy

Authors (year)	Country	Type of cancer, organ affected, stage	Treatment	Definition of adherence	Characteristics of sample	Method for assessing adherence	Adherence measurement time	Adherence results	Determinants of non-adherence	Conclusions/discussion
Lebovits <i>et al.</i> (1990)	USA	Breast	Endoxan – 1st chemo	Adherence cut-off point set between 90% and 110% of prescribed intakes (called behavioural adherence) and total non-adherence if <90% of medication taken in 26 weeks of treatment	<ul style="list-style-type: none"> <li>* n = 51 women</li> <li>* Mean age: 53 years</li> </ul>	Indirect measures Interview conducted by physician: medical data collected on 1st interview; subsequent interviews: assessment of toxicity, adherence, and following treatment instructions, etc.	<ul style="list-style-type: none"> <li>* 5 interviews (1st day of treatment, weeks 1, 4, 13 and 26)</li> </ul>	<ul style="list-style-type: none"> <li>* 53% behavioural adherence</li> <li>* 57% intake adherence</li> <li>* 24% over-adherence</li> <li>* 16% under-adherence</li> <li>* 4% complete stopping</li> </ul>	<ul style="list-style-type: none"> <li>* Taking 2 treatments instead of 1</li> <li>* Lower income</li> <li>* Decrease over time</li> </ul>	<ul style="list-style-type: none"> <li>* Anticancer treatments taken at home may be seen as 'less medical' by patient</li> <li>* Less compliant patients exhibit more depressive disorders</li> <li>* Difficulty managing chemotherapy and its toxicity are associated with negative representations of treatment</li> <li>* Self-report measures and risk of underestimation of true adherence</li> <li>* Difficult to generalise results to all stages of cancer</li> </ul>
Lee <i>et al.</i> (1992)	Great Britain	Lymphomas	Oral chemotherapy	<ul style="list-style-type: none"> <li>* No definition given</li> <li>* Difficult to choose a cut-off above which non-adherence to this molecule is risky for patient</li> </ul>	<ul style="list-style-type: none"> <li>* n = 25 (52% men)</li> <li>* Mean age: 58 years</li> </ul>	Indirect measures MEMS	Over 6 weeks	100% adherence	<ul style="list-style-type: none"> <li>* With the number of intakes</li> <li>* Nausea</li> <li>* Irregular intake hours</li> </ul>	<ul style="list-style-type: none"> <li>* Very good adherence in this study seems to argue in favour of using oral chemotherapy</li> <li>* Advantages in terms of health costs and convenience of oral route for patients</li> </ul>
Lee <i>et al.</i> (1993)	Great Britain	Lung cancer	Celltop	Adherence cut-off set at 100% of prescribed intakes	<ul style="list-style-type: none"> <li>* n = 14 (21% women)</li> <li>* Mean age: 62 years</li> </ul>	Indirect measures MEMS	Over 6 weeks	Total adherence: 93.2%	<ul style="list-style-type: none"> <li>* Nausea associated with poor adherence to scheduled intake times</li> <li>* Poorer adherence for number of daily intakes linked to longer time since diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>* Adherence not linked to quality of life or to secondary effects of oral treatment</li> <li>* Adherence is better with simpler treatment schedules (in terms of number of treatments and number of daily intakes)</li> <li>* Small sample size</li> <li>* No definition of adherence cut-off</li> </ul>
Lee <i>et al.</i> (1996)	Great Britain	Advanced ovarian cancer in relapse	Hexastat	Adherence cut-off set at 100% of prescribed intakes	<ul style="list-style-type: none"> <li>* n = 11</li> <li>* Mean age: 58 years</li> </ul>	Indirect measures MEMS	Over 6 weeks	Total adherence: 97.4%	<ul style="list-style-type: none"> <li>* Poor quality sleep linked to increased intake irregularity in terms of time of day and number of intakes per day</li> </ul>	<ul style="list-style-type: none"> <li>* Good compliance with Hexastat and good assumed acceptability for patient</li> <li>* Higher overall adherence rate than found in most studies on this topic</li> <li>* Small sample size</li> </ul>

**Table 1.** *Continued*

Authors [year]	Country	Type of cancer, organ affected, stage	Treatment	Definition of adherence	Characteristics of sample	Method for assessing adherence	Adherence measurement time	Adherence results	Determinants of non-adherence	Conclusions/discussion
Uematsu <i>et al.</i> (1996)	Japan	Colorectal Cancer	5-FU	Adherence cut-off is the limit for biochemical detection of 5-FU in hair	<ul style="list-style-type: none"> <li><math>n = 55</math> (47% women)</li> <li>Mean age: 57 years</li> </ul>	<p>Direct measures</p> <p>Biological measures taken from hair sample</p>	Single measure at 6 months (end of treatment)	Correct adherence rate for 60% of patients		<ul style="list-style-type: none"> <li>Particular situation in Japan, where patients still frequently not told they have cancer, with a potential impact on adherence</li> <li>High inter-individual variability in measure used</li> </ul>
Sadahiro <i>et al.</i> (2000)	Japan	Colorectal cancer	UFT (1 year period)	Adherence cut-off set at a given concentration of substance in urine; fewer than 3 omissions per week measured on a 3-point scale	<ul style="list-style-type: none"> <li><math>n = 87</math> (30% women)</li> <li>Mean age: 57 years</li> </ul>	<p>Indirect measures</p> <p>Interview by physician on a 3-point scale:                      (1) medication taken (or forgotten twice at most);                      (2) treatment not taken because of toxicity;                      (3) forgotten at least 3 times in 1 week</p>	<ul style="list-style-type: none"> <li>Every 3 months (by physician and self-reported)</li> <li>Urine sample at 3, 6, and 9 months</li> </ul>	<p>Adherence:</p> <ul style="list-style-type: none"> <li>At 3 months: 94%</li> <li>At 6 months: 95%</li> <li>At 9 months: 98%</li> </ul>		<ul style="list-style-type: none"> <li>High inter-individual variability in measure used</li> </ul>
Klein <i>et al.</i> (2006)	USA	Myelo-dysplastic syndrome	Hycamtin	Adherence cut-off set at 100% of prescribed intakes using MEMS	<ul style="list-style-type: none"> <li><math>n = 90</math> (sex ratio not specified)</li> <li>Mean age: 70 years</li> </ul>	<p>Indirect measures</p> <p>MEMS</p>	Each of 6 cycles	<ul style="list-style-type: none"> <li>90% good adherence (correct number of intakes)</li> <li>55% correct adherence (for time interval between intakes)</li> </ul>	<ul style="list-style-type: none"> <li>No significant difference in adherence between the 2 intake schedules</li> </ul>	<ul style="list-style-type: none"> <li>Importance of repeated, ongoing communication between caregiver and patient in explaining overall adherence rate, deemed 'excellent'</li> </ul>
MacIntosh <i>et al.</i> (2007)	Canada	Solid tumours (84% are gastro-intestinal)	Xeloda	Adherence cut-off set at 100% of prescribed intakes, according to type of dispenser (by cycle vs. by day)	<ul style="list-style-type: none"> <li><math>n = 25</math> (60% women)</li> <li>Mean age: 64 years</li> </ul>	<p>Indirect measures</p> <p>MEMS</p>	Each of 6 cycles	<ul style="list-style-type: none"> <li>87% correct adherence on cycle 1</li> <li>78% correct adherence on cycle 2</li> </ul>	<ul style="list-style-type: none"> <li>No adherence difference between the 2 types of dispensers tested, but preference for dispenser that divides treatment into daily doses</li> <li>Small sample size, and multivariate analyses impossible</li> <li>Measures taken over a short period, possibly explaining high adherence rat.</li> <li>Difficult to generalise to other types of oral chemotherapy given high variability across intake modes</li> </ul>	

Mayer <i>et al.</i> (2009)	USA	Locally advanced or metastatic breast cancer	Xeloda and Iressa	Cut-off for adherence set at 80% of prescribed intakes, using MEMS	* <i>n</i> = 19 (100% women) * Mean age: 47 years	Indirect measures	MEMS	* Every visit, for the entire duration of treatment (average: 5 times in 15 weeks)	For both methods: * 95% correct adherence * 44% with at least one over-use mistake	* Results underline need for psycho-educational intervention aimed not only at improving adherence but also at assessing it * Cases of poor adherence do not seem to have an impact on treatment effectiveness * Cases of over-adherence in this study in fact have higher adherence rates than the patient mean, thereby decreasing the generality of the results * According to authors, the high non-adherence rate is surprising, since variables favouring adherence were present in this study (serious illness, effective treatments, low toxicity, advantages of oral route, etc.) * Adherence is over-evaluated by other parties (physician and family) * Measures limited to 90 days * Recruitment bias (study participants more compliant than patients refusing to participate)
Noens <i>et al.</i> (2009)	Belgium	Chronic myeloid leukaemia	Glivec	Patient considered non-adherent if one negative response on the 4-point Basel Assessment of Adherence Scale	* <i>n</i> = 202 (55% men) * Mean age: 57 years	Indirect measures	Inclusion and month 3	<i>BAAS at baseline:</i> * 69.3% adherence * 16.1% with an occasional missing intake at treatment onset * 1.2% had fewer intakes * 77.8% adherence for time lapse between 2 intakes <i>BAAS at 3 months:</i> * 67.3% adherence * 13.3% with an occasional missing intake * 1.8% had fewer intakes * 74.7% adherence for time lapse between 2 intakes <i>Adherence at appointment times:</i> * 89.4% at study inclusion * 86.6% at 3 months <i>Pill counting:</i> * 90.9% correct adherence between inclusion and 3rd month	* Old age * Diagnosis long time ago * Living alone * Being a man * Lengthy treatment * Treatment dose above 600 mg/day * Physician has little experience (in years) * Patient has less knowledge of his/her illness and treatment * Low degree of long-term self-efficacy	

Table 1. Continued

Authors [year]	Country	Type of cancer, organ affected, stage	Treatment	Definition of adherence	Characteristics of sample	Method for assessing adherence	Adherence measurement time	Adherence results	Determinants of non-adherence	Conclusions/discussion
Decker <i>et al.</i> (2009)	USA	Solid tumours (breast, lung, colon, etc.)	Xeloda, Endoxan and Tyverb	<ul style="list-style-type: none"> <li>Assess effectiveness of intervening via a telephone call followed by an end-of-treatment interview and a consultation with a nurse if poor adherence is noted</li> <li>Adherence cut-off based on several measures:                             <ol style="list-style-type: none"> <li>repeated telephone interviews, (2) non-adherence if one extra or one too few pills taken than prescribed, (3) comparison of results with various medical data (dose adjustment, toxicity, reduction of posology, etc.)</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li><math>n = 30</math> (94% women)</li> <li>Mean age: 60 years</li> </ul>	Indirect measures	<ul style="list-style-type: none"> <li>Interviews: at inclusion time and at 10 weeks (end of treatment)</li> <li>Every week via automatic telephone call (measuring adherence over the past 7 days)</li> </ul>	<ul style="list-style-type: none"> <li>Pill counting:                             <ul style="list-style-type: none"> <li>77% overall adherence (average of measure at inclusion time and at 10 weeks)</li> <li>71% explained by forgetting</li> <li>20% missed a single intake (amount taken between 68% and 93% of prescribed dose)</li> <li>3% no intakes</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>No association between adherence and variables like beliefs about treatment, level of depression and functional level of patients</li> <li>Generalisability of results limited because sample composed mainly of white women with breast cancer</li> </ul>	<ul style="list-style-type: none"> <li>First study to test effectiveness of intervening via a telephone call about adherence</li> <li>Effectiveness of automated telephone calls with intervention by a nurse about adherence</li> <li>No association between adherence and variables like beliefs about treatment, level of depression and functional level of patients</li> <li>Generalisability of results limited because sample composed mainly of white women with breast cancer</li> </ul>
Partridge <i>et al.</i> (2010)	USA	Solid tumours (breast, colon)	Xeloda	Cut-off at 80%	<ul style="list-style-type: none"> <li><math>n = 167</math></li> <li>Mean age: 71 years</li> </ul>	Indirect measure	On 6 treatment cycles	<ul style="list-style-type: none"> <li>22% are non-adherent</li> <li>At least one forgotten dose in 66% of patients.</li> <li>Over-adherence in 11%</li> </ul>	<ul style="list-style-type: none"> <li>Do not have a ganglion target</li> <li>To have had a mastectomy</li> </ul>	<ul style="list-style-type: none"> <li>No link between over-adherence and 3- to 4 stage toxicity</li> <li>No link between adherence and decreased survival</li> <li>Limits: patients were low socio-economic level</li> <li>Moreover, higher adherence in clinical trials</li> </ul>
Bhattacharya <i>et al.</i> (2012)	UK	Solid tumours (breast, colon)	Xeloda	Cut-off at 100%	<ul style="list-style-type: none"> <li><math>n = 43</math> (56% women)</li> <li>Mean age: 65 years</li> </ul>	Indirect measure	Not defined	<ul style="list-style-type: none"> <li>18.7% forgot to take medication</li> <li>4% of sus-adherence</li> </ul>	No identified determinants	<ul style="list-style-type: none"> <li>Focus on education about treatment and behaviour of intentional non-adherence.</li> <li>Limits: limited sample size</li> </ul>
Simons <i>et al.</i> (2011)	Germany	Solid tumours (breast, colon)	Xeloda	Cut-off at 80%	<ul style="list-style-type: none"> <li><math>n = 48</math> (77% women)</li> <li>Mean age: 56 years</li> </ul>	Indirect measure	On 7 treatment cycles	<ul style="list-style-type: none"> <li>10.4% had &lt;80% of global adherence</li> <li>16.7% had &lt;90% of global adherence</li> <li>18.8% daily adherence less of 90%</li> </ul>	<ul style="list-style-type: none"> <li>Need to better identify the patients who need to improve adherence</li> <li>Limit: definition of the cut-off is arbitrary because no clinical efficacy demonstrated</li> </ul>	<ul style="list-style-type: none"> <li>Need to better identify the patients who need to improve adherence</li> <li>Limit: definition of the cut-off is arbitrary because no clinical efficacy demonstrated</li> </ul>

Spiegelstra <i>et al.</i> (2013)	USA	Solid tumours (breast, lung, colon)	Diverse (Xeloda and Tarceva at least)	Cut-off at 80% for 7 days	<ul style="list-style-type: none"> <li>* <math>n = 119</math> (69% women)</li> <li>* Mean age: 60 years</li> </ul>	Indirect measure	<ul style="list-style-type: none"> <li>* Self-reported</li> <li>* Register of pharmacy office</li> </ul>	<ul style="list-style-type: none"> <li>* Interview at inclusion and at the end of study (10 weeks)</li> <li>* Measurement at 8 weeks</li> <li>* A weekly measurement about the 7 last days</li> </ul>	<ul style="list-style-type: none"> <li>* Adherence: 58% 13% for dose decrease</li> <li>* 20% of over-adherence</li> </ul>	<ul style="list-style-type: none"> <li>* Protocol complexity</li> <li>* No association with depression, toxicity, gender and age</li> </ul>	<ul style="list-style-type: none"> <li>* Education focus on side-effects gestion and way to discuss it with the oncologist</li> <li>* Education must be begin before the initiation of the treatment</li> </ul>
Khandelwal <i>et al.</i> (2012)	USA	Solid tumours (breast, colon)	Sutent, Nexavar and Tarceva	Cut-off at 100%	<ul style="list-style-type: none"> <li>* <math>n = 377</math></li> </ul>	Indirect measure	Possession index determined by patients themselves	At 6 months	<ul style="list-style-type: none"> <li>* 99% at 1 month</li> <li>* 64% at 3 months</li> <li>* 43% at 6 months</li> <li>* 51.2% persistence at 3 months, and 23.8% at 6 months</li> </ul>	<ul style="list-style-type: none"> <li>* Toxicity</li> </ul>	<ul style="list-style-type: none"> <li>* Adherence monitoring by an interventional action improve a better toxicity gestion and less hospitalisation</li> </ul>
Gebbia <i>et al.</i> (2013)	Italy	Non-small-cell lung cancer	Tarceva (Erlotinib)	Cut-off definition: <ul style="list-style-type: none"> <li>* 100-95%: missing taking medication for 3 days during 2 months</li> <li>* 94-90%: missing taking medication for 6 days</li> <li>* &lt;90%: missing taking medication for at least 6 days</li> </ul>	<ul style="list-style-type: none"> <li>* <math>n = 150</math> (33% women)</li> <li>* Mean age: 66 years</li> </ul>	Indirect measure	<ul style="list-style-type: none"> <li>* Self-reported: BAAS</li> <li>* Visual analogue scale</li> <li>* Pill count</li> </ul>	Monthly	<ul style="list-style-type: none"> <li>* BAAS: 22% of had adherence</li> <li>* BAAS: 7% of patients with &lt;90% adherence</li> <li>* 17% of non-adherence by pill count</li> </ul>	<ul style="list-style-type: none"> <li>* Toxicity</li> </ul>	<ul style="list-style-type: none"> <li>* Better treatment response in patients in the intervention group</li> <li>* Limits: possible over-estimation with the using of visual analogue scale</li> <li>* Selection bias: better adherent have accepted easier to the study participation</li> </ul>
Darkow <i>et al.</i> (2007)	USA	Chronic lymphoid leukaemia	Glivec (Imatinib)	Cut-off definition: <ul style="list-style-type: none"> <li>* Very high: 95-100%</li> <li>* High: 90-95%</li> <li>* Intermediate: 50-90%</li> <li>* Low: 0-50%</li> </ul>	<ul style="list-style-type: none"> <li>* <math>n = 267</math> (43% women)</li> <li>* Mean age: 50 years</li> </ul>	Indirect measure	<ul style="list-style-type: none"> <li>* Index of possession</li> </ul>	At 12 months	<ul style="list-style-type: none"> <li>* 20% had &lt;50% of global adherence</li> <li>* 45% had 100% adherence</li> <li>* 31% interrupted treatment during at least 30 days</li> </ul>	<ul style="list-style-type: none"> <li>* Be a woman</li> <li>* Polymedication</li> <li>* Co-morbidities</li> <li>* Increase health costs</li> </ul>	<ul style="list-style-type: none"> <li>* Limits: data from register of disease insurance so generalisation is difficult for not insured patients</li> </ul>
Sommers <i>et al.</i> (2012)	USA	Digestive cancer	Divers	No defined cut-off	<ul style="list-style-type: none"> <li>* <math>n = 30</math> (23% women)</li> <li>* Mean age: 53 years</li> </ul>	Indirect measure	<ul style="list-style-type: none"> <li>* Self-reported: MMAS-8 maximum score at 8</li> </ul>	<ul style="list-style-type: none"> <li>* Only one measurement during the first treatment cycle</li> </ul>	<ul style="list-style-type: none"> <li>* 30% of patients did not correctly complete their diary</li> <li>* Mean MMAS: 7.89</li> </ul>	<ul style="list-style-type: none"> <li>* Nurse interventions are good</li> <li>* Limits: higher adherence could be explained by the fact that measure was at the beginning of treatment</li> <li>* Diary could be not adapted for the adherence measurement</li> </ul>	

Table 1. Continued

Authors [year]	Country	Type of cancer, organ affected, stage	Treatment	Definition of adherence	Characteristics of sample	Method for assessing adherence	Adherence measurement time	Adherence results	Determinants of non-adherence	Conclusions/discussion
Ganesan <i>et al.</i> [2011]	India	Chronic lymphoid leukaemia	Glivec (Imatinib)	Non-adherence if there was an interruption of at least 1 week	* <i>n</i> = 516 (66.5% women) * Mean age: 35 years	Indirect measure * Pill count at each visit to prescribing doctor	* Mean follow-up of 39 months	* 29.6% of voluntary non-adherence	* No identified determinants among age, gender, socio-economic status and disease stage	* In multivariate analyses: one determinant of prognosis, i.e. the voluntary non-adherence * No-adherence for other reasons (doctor choice) did not predict the median survival * Limitations: survival and duration of non-adherence not taken in count
Moon <i>et al.</i> [2012]	South Korean	Chronic lymphoid leukaemia	Glivec (Imatinib)	Cut-off at 100%	* <i>n</i> = 114 (ratio of women to men not known) * Mean age: not known	* Type of measurement not mentioned * Measurement index: persistence (on 1 year); dose-observance; global observance	* Survival at 3 years	* 91.8% persistence at 3 years * 96.5% of patients respect the dose * Total observance persistence and dose: 88%. * Decreased adherence with time	Not defined	* 2-group trials. Patients with intervention are more adherents than patients of group without intervention * Persistence is the main determinant revealed by the intervention * Relation doctor-patient increased. Consequently, easier discussion about toxicity and adapt the dose if necessary

MEMS, Medication Event Monitoring System; BAAS, Brief Adult Assessment Scale; 5-FU, 5-fluorouracil.

Sutent, etc.), forbidden foods (avoidance of foods containing fat for Nexavar, no grapefruit for Tyverb), pill storage mode (in a cool place or away from a light source for certain molecules), what to do in case of forgetting to take medication, how to handle secondary effects, and management of other treatments (e.g. analgesics, antiemetics, corticosteroids). Hence, much new and highly varied information must be retained. Therapy education seems essential for improving the effectiveness of the information delivered, but considerable improvement is needed in this area, and, if oral treatment continues to grow, many gaps need to be filled.

Among the factors generally associated with adherence, the patient's psychological distress is important. In the Lebovits *et al.* (1990) study, less-adherent patients usually exhibited the greatest number of depressive symptoms. In line with the literature in domains other than cancer, socio-demographic variables seem to have little effect on adherence. Only the study by Noens *et al.* (2009) indicated a negative association of age and adherence. Length of treatment is often found associated with adherence: four of our articles mentioned length of treatment but with divergent results, and some authors (Klein *et al.* 2006; MacIntosh *et al.* 2007), although without studying this parameter *per se*, mentioned a negative association of adherence and length of treatment (Lebovits *et al.* 1990; Lee *et al.* 1993; Noens *et al.* 2009).

Another aspect is the number of times medication has to be taken daily: the greater the number, the poorer the adherence. In the Lee *et al.* (1992) study, adherence tended to decline beginning with three intakes per day. Finally, concerning the doses ingested, Noens *et al.* (2009) found that a high posology was associated with poor adherence. Lee *et al.* (1996) had similar findings, showing that poor-quality sleep had a negative impact with irregular hourly or daily intake schedules. Lack of sleep is thought to be related to irritability, fatigue or anxiety among patients, all of which are likely associated with risk of forgetting to take medicine.

The toxicity level of a drug can hinder the ability to adapt psychologically to the treatment; Lebovits *et al.* (1990) found that this factor may jeopardise adherence (by eliciting intake-reducing behaviours or even temporary stopping). Some studies also found this link (Lee *et al.* 1992; Decker *et al.* 2009; Noens *et al.* 2009). The packaging of oral chemotherapy should also be considered. Among the wide variety of packaging modes, some are poorly suited to the prescribed intake protocol (Ranchon *et al.* 2009). Finally, drug absorption by the body is influenced by the nature of the patient's diet and the amount of time between eating and medicine intake (Singh & Malhotra 2004).

Finally, most of our 21 articles described an indirect methodology to assess adherence. Direct measures are based on medical criteria and thereby provide objective, standardised, reliable data that are independent of the subjective opinions of patients. Direct measures do not rely on markers specific to each kind of treatment. However, their degree of objectiveness can be disputed, because each person's body reacts individually. This situation raises the question of whether standardised measures should be used. Indeed, the dose to be prescribed for a given medication is still mostly determined by individual differences in absorption capacity, distribution and metabolism. In this context, the blood level of a drug is likely a useful tool. For example, it can be used to readjust the prescribed quantity to reduce secondary effects due to overdose, especially because secondary effects themselves can lead to poor adherence. The effects have the advantage of being objective but the disadvantage of being considered invasive by the patient. In addition, direct measures involve some technical difficulties and discomfort for the patient. Finally, identifying pharmaceutical substances in the organism cannot describe the frequency and regularity of medicine intake and offers no explanation for the reasons for non-adherence (Besch 1995). Indirect measures are easier to implement for medical or non-medical practitioners than are biological analyses and provide more detailed data than objective measures, particularly in terms of the patient's opinion and the perceptions of healthcare staff about patient adherence. However, patients may say what their physicians want to hear and consequently overestimate their adherence to medication (Holzemer *et al.* 1999). Indeed, patients who self-report are often considered good adherents. However, such methods cannot grasp the full complexity of patient behaviour with respect to their treatment. One can legitimately assume that the tools used (MEMS, self-administered questionnaires, biological tests) do not capture this complexity. The search for causes of adherence must be accompanied by a search for understanding (i.e. combined with a more interpretative and comprehensive approach).

## CONCLUSIONS

Non-adherence with therapy is a new but common problem in treating cancer with oral antineoplastic agents. Non-adherence and care disparities must be recognised in clinical practice with a focus on high-risk individuals to improve patient adherence.

With the advent of new treatment possibilities, adherence has become a key issue for oncologists, because it conditions the efficacy of chemotherapy. Therapeutic

adherence is connected to patient perceptions of changes in treatment and the disease. Therefore, patients' mental representations of chemotherapy are riddled with ambivalence: oral treatments, although considered more favourable than intravenous ones, incur multiple doubts about their effectiveness and significance.

Further research is needed in this field, especially if oral chemotherapy continues to develop. Some future

studies could compare therapeutic adherence across drug-administration modes. Others could work on devising specific tools for measuring adherence to oral antineoplastic agents, to reveal particularities. Adherence is a dynamic phenomenon, so more longitudinal studies would be useful for investigating this new issue.

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