


# Adherence to oral chemotherapy: Evidence from a randomised clinical trial

Ada Ghiggia<sup>1,2</sup> | Alessandra Bianco<sup>3</sup> | Lorys Castelli<sup>2</sup>  | Francesca Baratta<sup>4</sup> |  
Nadia Birocco<sup>5</sup> | Matilde Scaldaferrì<sup>3</sup> | Paola Milla<sup>4</sup> | Valentina Tesio<sup>2</sup> |  
Stefano Rosso<sup>6</sup> | Riccardo Torta<sup>1</sup> | Paola Brusa<sup>4</sup> | Francesco Cattel<sup>3</sup>

<sup>1</sup>Clinical Psychology Unit, Città della Salute e della Scienza, Turin, Italy

<sup>2</sup>Department of Psychology, University of Turin, Turin, Italy

<sup>3</sup>Hospital Pharmacy, Città della Salute e della Scienza, Turin, Italy

<sup>4</sup>Department of Drug Science and Technology, University of Turin, Turin, Italy

<sup>5</sup>Department of Oncology, Città della Salute e della Scienza, Turin, Italy

<sup>6</sup>Piedmont Cancer Registry, Città della Salute e della Scienza di Torino, Turin, Italy

## Correspondence

Lorys Castelli, Department of Psychology, University of Turin, Via Po 14, 10123, Turin, Italy.

Email: lorys.castelli@unito.it

## Funding information

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

## Abstract

**Objective:** To evaluate the efficacy of a reinforcement message (RM) administered by a hospital pharmacist on adherence, through a randomised study involving patients undergoing oral chemotherapy from which an objective outcome measure and patients' subjective opinions were collected. A secondary aim was to detect which psychological or clinical factors influence adherence.

**Methods:** Forty patients were enrolled and randomised to an experimental group (EG) or a control group (CG). The EG received a 10-minute RM provided by a hospital pharmacist with a doctor and a nurse. The CG received the standard of care. To measure adherence, plasma drug concentration and subjective evaluation were taken during the visits, in addition to a psychological assessment (coping strategies, psychological distress and personality traits).

**Results:** The EG reported higher drug levels and a statistically significant higher mean score on the subjective evaluation. A linear regression model highlighted statistically significant differences in the plasma drug concentration, after considering toxicity and dose reduction and controlling for the Reward Dependence Scale of the Temperament and Character Inventory between the EG and the CG.

**Conclusion:** Adequate information and education on the therapy, using an RM strategy provided by a hospital pharmacist, seems to positively influence adherence to the treatment.

## KEYWORDS

cancer care, hospital pharmacist, medication adherence, oral chemotherapy, personality traits, temperament and character inventory

## 1 | INTRODUCTION

For cancer patients, taking oral medications at home has many positive aspects compared with hospital intravenous administration, especially in terms of a better quality of life. However, it can involve the risk of poor therapeutic adherence (Neuss et al., 2013).

Medication adherence is defined as "the degree or extent of conformity (most appropriately a percentage) to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency" (Cramer et al., 2008). Moreover, medication non-adherence negatively impacts treatment efficacy (exacerbating side effects or worsening the prognosis) and the social

and economic costs of even the most advanced healthcare systems by wasting healthcare resources (Bouwman et al., 2017; Hall et al., 2016).

Medication adherence includes a variety of complex elements. Some factors are strictly medical, such as the type of pathology or the presence of comorbidity, while others are strictly psycho-social, such as socio-demographic, psychological and personality characteristics (Brown & Bussell, 2011; Lima et al., 2018; Tominaga et al., 2018). Personality traits seem to play a key role in how individuals perceive and face their diseases. High levels of neuroticism and maladaptive coping strategies seem to predict a poor adaptation to illness (Edwards et al., 2010; Jerant et al., 2011). However, the complexity of the treatment (i.e. the frequency of administration, timing of pill taking, side effects) can negatively affect medication adherence. Several studies have taken into consideration the implementation of information strategies to optimise the medication adherence of cancer patients undergoing oral therapy. In fact, the "2013 Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards Including Standards for the Safe Administration and Management of Oral Chemotherapy" states that patients should receive adequate information on their treatment plan, including written documentation on the goals and planned duration of therapy and information on drugs, including possible short- and long-term adverse effects (Neuss et al., 2013). An interesting method for achieving this purpose is to enhance the clinical staff by implementing the role of a hospital pharmacist. Previous interventions have been developed to introduce hospital pharmacists to communicate the information necessary for the therapy management, either in written form (e.g. a leaflet) or a verbal reinforcement message (RM; Gatwood et al., 2017; Sanii et al., 2016; Zerillo et al., 2018).

However, the majority of these studies showed important limitations. They did not use an objective measure of drug adherence, and they rarely investigated psychological factors as predictors of adherence (Felton et al., 2016; Haynes et al., 2008).

Thus, we planned a randomised study involving patients undergoing oral chemotherapy. Patients with lung carcinoma (LC), hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC) were recruited to evaluate the efficacy of an RM administered by a group of specialists, including a hospital pharmacist, in improving medication adherence. The main aim of the study was to test the efficacy of the RM by investigating: (a) the plasma drug concentration, as an objective outcome measure, and (b) the opinion of the patients through subjective measures.

The secondary aim was to detect which factors influence adherence among a set of operative measured variables encompassing patient characteristics, clinical determinants and psychological aspects, such as coping strategies, temperament and character.

## 2 | MATERIALS AND METHODS

### 2.1 | Trial design

We performed a single-centre randomised clinical trial to test the efficacy of an RM for improving patient adherence to oral chemotherapy. The study was approved by the Ethics Committee of San Giovanni Battista Hospital in Turin, Italy, and was conducted in accordance with the Declaration of Helsinki. Eligible patients were older than 18 years of age and scheduled to start treatment with sorafenib, erlotinib or sunitinib, depending on the specific pathology (see Pharmacological treatment). Patients were recruited from among those treated by the Oncology Department between June 2011 and August 2014. Forty patients consented to participate in the trial and were then randomised to one of the two study groups. A maximum of 10 subsequent visits was allowed for about a 1-year follow-up period.

The Mini-Mental State Examination was administered to exclude patients with cognitive impairment, such as those who reported a score below the threshold of 24 (Measso et al., 1993). After recruitment and signature of the consent form, the patients were blindly randomised into the two groups, the experimental group (EG) or the control group (CG), in three blocks according to the 3 oral chemotherapies. Randomisation was performed by an external centre that was not involved in the patients' treatment.

The first visit was dedicated to recruitment and basal evaluation (Figure 1). After one week, a second visit was scheduled to collect psychological data and provide pharmacological recommendations. The EG received a 10-minute RM session that was provided by the hospital pharmacist in the presence of a doctor and a nurse. The CG received the standard of care, with the usual recommendations provided by the doctor and nurse. In addition to evaluating the patients' perceived information and therapy concerns, the first determination of plasma drug concentration (main outcome measurement) was taken at the third visit, after the start of treatment. The following visits took place at regular intervals, providing the standard of care and taking into account any specific patient needs.

### 2.2 | Pharmacological treatment

The patients with HCC were treated with sorafenib (Keating, 2017); the LC patients received erlotinib (Rosell et al., 2012); patients with RCC were prescribed sunitinib (Motzer et al., 2012). The study did not provide any kind of intervention on the administration or dosage of the medicine (erlotinib 150 mg/day, 1-2 hr before meals; sorafenib 400 mg/day, 2 times a day after meals; sunitinib 50 mg/day for 4 weeks, followed by a 2-week break). Compared with the normal procedures, the study only included a larger volume of blood samples during the follow-up visits.

At each visit, patients were evaluated on haematological parameters and related symptoms. Each sign/symptom at the visit was

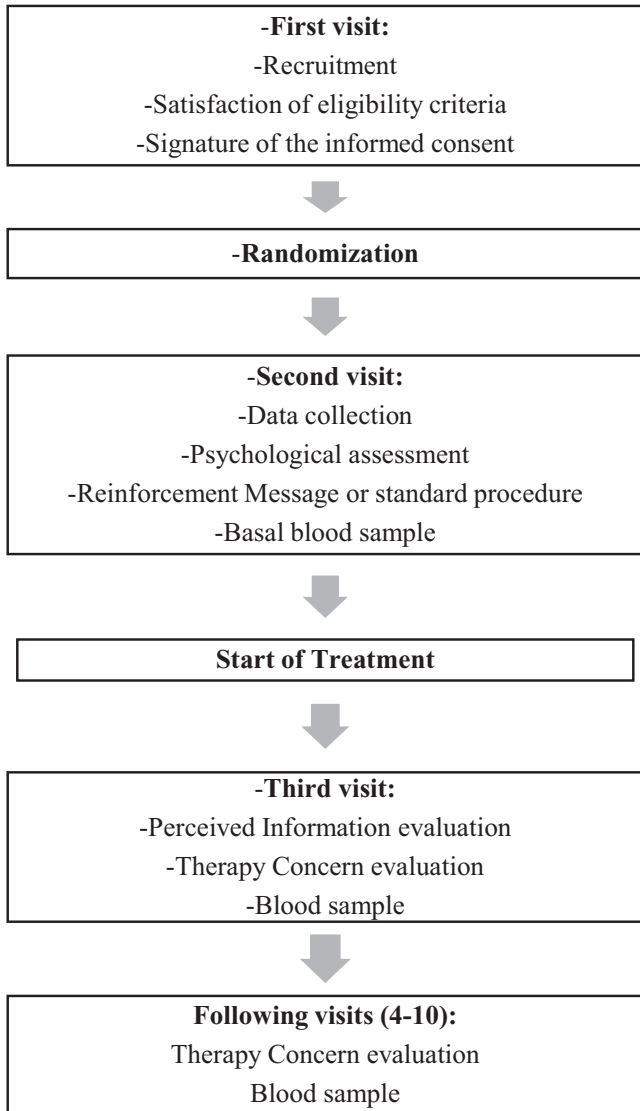


FIGURE 1 Flow chart of the study process

then scored on a 0 (absence) or 1 (presence) scale, and the total score was calculated as a sum of single scores (total toxicity score—TTox). Furthermore, drug dose reduction (yes/no) was taken into account.

### 2.3 | Reinforcement message (RM)

Four hospital pharmacists were involved in the study following a preliminary training in order to standardise their RM. After recruitment, during the second visit, the hospital pharmacist explained to the EG patients the importance of complying with the recommendation for the specific drug and its possible side effects. A leaflet was handed to the patients to ensure additional facilitation of the proper management of the prescribed therapy. So, every patient received the same message, obviously based on the type of drug. The leaflets concerned information related to how and when the drug should be taken, how to preserve it, which precautions should be adopted in the case of the consumption of other drugs or dietary supplements,

the possible adverse reactions, what to do in case there are interruptions in the treatment, and where to go for supplies. An easily understandable language was adopted to facilitate the enrolled patients' use of the leaflets. On average, the RM session was planned to last 10 min.

## 2.4 | Outcome measurements

### 2.4.1 | Determination of oral chemotherapy plasmatic concentrations

Blood samples (5 ml) were drawn before starting the therapy and then at the start of the 10 scheduled follow-up appointments. Samples were immediately centrifuged at 2,500 g for 10 min at 4°C, and the plasma was frozen and stored at -70°C until analysis. The outcome measure was evaluated as the difference in the blood concentration of drug metabolites during the 10 follow-up visits.

Sorafenib, erlotinib and sunitinib were analysed at room temperature by reversed-phase high-performance liquid chromatography with ultraviolet detection. The analysis was performed on a Symmetry C18 column (250 × 4.6 mm i.d., particle size 5 µm) equipped with a Symmetry C18 guard column supplied by Waters (Vimodrone, Milan, Italy) after a liquid-liquid extraction from the plasma samples, using a modification of previously reported procedures (Blanchet et al., 2009; Etienne-Grimaldi et al., 2009). The limit of quantitation (LOQ) was 20 ng/ml for sorafenib and erlotinib and 5 ng/ml for sunitinib.

### 2.4.2 | Psychological assessment

A psychological evaluation was performed during the second visit. Anxious and depressive symptomatology was assessed using the Hospital Anxiety and Depression Scale (HADS), with higher scores indicating higher severity of psychological distress (Castelli et al., 2009; Zigmond & Snaith, 1983).

A short Italian version of the Mental Adjustment to Cancer Scale (Mini-MAC) was administered to measure five different coping strategies: helplessness/hopelessness, anxious preoccupation, fighting spirit, cognitive avoidance and fatalism (Grassi et al., 2005).

The Italian version of the Temperament and Character Inventory (TCI) was used to assess the participants' personalities (Fossati et al., 2001). The TCI is a 240-item, true-false questionnaire that assesses personality by describing the four dimensions of Temperament (Harm Avoidance—HA, Novelty Seeking—NS, Reward Dependence—RD, and Persistence—P) and the three dimensions of character (Self-directedness—SD, Cooperativeness—C, and Self-transcendence—ST; Cloninger et al., 1994).

During the third and following visits (Figure 1), the patients' opinions were assessed through a subjective measure: an evaluation of the perceived information obtained during the medical visit was administered. We asked the patients to rate the fullness and adequacy

of the information about the side effects and treatment strategy, using four questions on a numeric rating scale (NRS) ranging from 1 (low) to 5 (very high). In addition, we evaluated the patients' therapy concerns with three questions about their level of concern over the oral administration, side effects and treatment efficacy with three NRSs ranging from 1 (not at all) to 10 (very much).

### 2.4.3 | Sample size

We estimated that a difference between the two groups in the mean standardised plasmatic drug concentration of the same dimension of its standard error (i.e. an effect size of 1) would be of clinical relevance. With a two-sided statistical test of 90% of power at the usual significance level of 5% to detect a clinically relevant difference, we required a minimum of 23 patients for each trial group. To maintain the balance of the randomisation of the two trial groups with the three drug blocks, we rounded the sample size to 8 patients per block, resulting in 24 patients for each trial group and 16 patients for each block for a total of 48 subjects.

### 2.5 | Statistical analysis

The values of the plasmatic drug concentrations taken at the beginning and then follow-up times were standardised and transformed into Z-scores to compare the intrinsically different values for the three drugs. The principal outcome was calculated as the difference between the two groups in the average standardised concentration, and it was evaluated with a t test for equal variances. In the case of abnormally distributed values, we also considered a non-parametric test (Mood test) to evaluate the difference between the trial groups (Mielke, 1976). Furthermore, the differences within the drug blocks were explored, comparing mean differences with their original values.

Possible reasons for changing attitudes towards drug intake or the diminishing effect of the RM over time (secondary aim) were explored with multivariate linear regression models, introducing as predictor variables, the psychological evaluation measured with the TCI scales. First, we set a base model regressing plasma mean drug concentration at each visit against the experimental/control group indicator and type of treatment. Then, we introduced each explanatory variable (Table 1) in a forward procedure, evaluating their significance and impact on regression estimates. If this test was passed and a variable was introduced in the model, we re-tested it, introducing further statistically significant variables in a backward procedure.

## 3 | RESULTS

We did not reach the full target sample size, because recruiting patients under sunitinib treatment proved to be more difficult than

expected. The recruitment stopped when a balance within the block had been reached with 4 patients in each trial group. The control group was composed of 20 men, whereas the experimental group had five women and 15 men. Between the second and third visits, three patients (two in the CG with erlotinib and sorafenib and one in the EG with sunitinib) dropped out of the study, leaving 37 patients with valid determinations.

Block randomisation worked properly, equally distributing patients with different characteristics between the control and experimental groups. Table 1 shows the t test results of the between-group differences according to patient characteristics and psychological evaluation at the second visit. Regarding psychological characteristics, only the MINI-MAC Scale on Fatalism showed a statistically significant difference between groups, suggesting greater use of a fatalistic coping mechanism by the control group, probably due to intra-individual differences, which did not emerge in the other scales.

### 3.1 | Main aim

The analysis of the primary outcome (plasma drug concentration of the follow-up visits; Table 2) showed that the EG maintained higher levels of erlotinib and sunitinib than did the CG. However, the difference did not reach statistical significance. Sorafenib plasma levels were slightly higher in the CG, but not significantly. The measured plasma levels were, in any case, comparable to the expected values, as reported in the literature (Awada et al., 2005; Britten et al., 2008; Hidalgo et al., 2001). After transforming the plasma concentration into Z-scores, using the overall mean and standard deviation as population parameters, the EG showed higher scores (higher plasma average). However, the difference with the CG was not statistically significant, suggesting comparable effectiveness in experimental and control groups.

The median of plasma concentration Z-scores was  $-0.067$  for the EG and  $-0.206$  for the CG, showing a more left-skewed distribution of drug plasma levels among the control group participants. Also, the Shapiro test for normality (Royston, 1982) showed that the plasma values were not normally distributed ( $W = 0.874$ ,  $p$ -value = 0.02 for the CG and  $W = 0.898$ ,  $p$ -value = 0.04 for the EG). Therefore, we used the Mood test to determine whether the plasma values in the CG were greater or lower than the plasma levels in the EG. The results showed that the ranked scores were significantly different between the two groups ( $Z = 1.67$ ,  $p$ -values = 0.04), with higher plasma levels of the oral drug in the EG. Moreover, a further difference was detected during the follow-up visits, in which EG patients exhibited a higher rate of symptoms, possibly due to drug toxicity. The TTox was 4.6 in the EG, statistically higher (Mood test  $p$ -value = 0.032) than the median of 3.9 in the CG. The difference was even larger in the sorafenib and sunitinib groups. Moreover, the EG reported a statistically significant higher mean score on the perceived information scale than that of the CG, suggesting the hospital pharmacist gave full and adequate information. However,

**TABLE 1** Socio-demographic, clinical and psychological characteristics in the experimental and control groups at baseline. Means ± standard deviations are listed

|                                       | Experimental group (N = 19) | Control group (N = 18) | t test (df); p-values        |
|---------------------------------------|-----------------------------|------------------------|------------------------------|
| Gender N (%)                          |                             |                        |                              |
| Male                                  | 14 (74%)                    | 18 (100%)              |                              |
| Female                                | 5 (26%)                     | 0 (100%)               |                              |
| Age (years)                           | 68.6 (6.92)                 | 65.8 (8.57)            | 1.116 (38); 0.27             |
| Weight (kg)                           | 74.33 (13.54)               | 73.03 (7.28)           | 0.34 (32); 0.74              |
| Body surface (m <sup>2</sup> )        | 1.83 (0.21)                 | 1.84 (0.11)            | 0.38 (31); 0.71              |
| ECOG—performance status               | 0.55 (0.69)                 | 0.45 (0.51)            | 0.523 (38); 0.60             |
| Toxicity scale                        | 3.9 (3.78)                  | 4.6 (2.64)             | <b>Z = 1.85<sup>†</sup>*</b> |
| Hospital Anxiety and Depression Scale | 11.05 (6.42)                | 9.32 (6.44)            | 0.573 (35); 0.57             |
| Total score, perceived information    | 18.94 (1.89)                | 16.28 (2.76)           | 2.87 (33); 0.01*             |
| Total score, therapy concern          | 8.24 (4.66)                 | 10.67 (5.81)           | -1.19 (33); 0.24             |
| Personality assessment—TCI            |                             |                        |                              |
| Novelty Seeking Scale                 | 42.83 (6.16)                | 44.31 (7.63)           | 0.56 (34); 0.57              |
| Harm Avoidance Scale                  | 53.84 (7.63)                | 58.34 (8.84)           | 1.52 (32); 0.13              |
| Reward Dependence Scale               | 45.63 (9.17)                | 43.32 (7.33)           | 0.94 (34); 0.35              |
| Persistence Scale                     | 43.25 (8.94)                | 41.87 (9.11)           | 0.29 (34); 0.76              |
| Self-Directedness Scale               | 52.22 (6.46)                | 48.99 (7.88)           | 1.40 (34); 0.17              |
| Cooperativeness Scale                 | 49.98 (8.48)                | 46.73 (7.18)           | 0.96 (34); 0.34              |
| Self-Transcendence Scale              | 44.76 (9.81)                | 43.60 (11.76)          | 0.60 (34); 0.55              |
| Coping strategies—MINI-MAC            |                             |                        |                              |
| Helpless/Hopeless Scale               | 1.63 (0.56)                 | 1.86 (0.72)            | 1.23 (35); 0.22              |
| Anxiety Preoccupation Scale           | 2.28 (0.63)                 | 2.26 (0.62)            | 0.05 (35); 0.95              |
| Fighting Spirit Scale                 | 3.35 (0.67)                 | 2.93 (0.93)            | 1.59 (35); 0.11              |
| Cognitive Avoidance Scale             | 2.79 (0.91)                 | 2.57 (0.85)            | 0.93 (35); 0.36              |
| Fatalism Scale                        | 3.16 (0.58)                 | 2.79 (0.53)            | <b>2.27 (35); 0.02*</b>      |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MINI-MAC, Mental Adjustment to Cancer Scale; TCI, Temperament and Character Inventory.

† Mood test.

\* *p*-values < 0.05.

no differences between the groups were found in the therapy concern scores (Table 1).

### 3.2 | Secondary aim

Unlike the Reward Dependence Scale (TCI), the demographic (age and sex), clinical (weight, body surface, ECOG) and psychological variables (HADS, MINI-Mac, TCI) did not correlate with plasma drug concentration (dependent variable). Therefore, they were no longer included in the regression analyses.

A linear regression model was run in order to test the difference in plasma drug concentrations between the study groups, considering toxicity and dose reduction and controlling for one of the temperament scales of the TCI, the Reward Dependence Scale. The missing values of analysed variables were treated with list-wise deletion, reducing the number of valid determinations to 157 in the final model. After adjusting for TTox, dose reduction and the Reward Dependence

Scale, the difference in the plasma drug concentration between the EG and the CG emerged as statistically significant (Table 3).

## 4 | DISCUSSION

Our study aimed to investigate the effect of a targeted RM strategy on oral chemotherapy adherence in cancer patients. In terms of the objective outcome measure, our analysis of the plasma concentration showed that the patients who received information from the hospital pharmacist, that is the RM, maintained higher drug levels than did the control group, which was informed by the nurse, as is the standard of care. Unfortunately, after the first 3 visits, the number of patients who discontinued the therapy grew consistently, limiting the possibility of making further time-trend analyses due to an insufficient number of observations.

The EG patients reported having received more adequate and complete information regarding the side effects and treatment strategies

**TABLE 2** Differences in the median plasma concentration of the follow-up visits after intervention between experimental and control groups

| Oral chemotherapy  | Experimental group (N = 19) (µg/ml) | Control group (N = 18) (µg/ml) | Difference between trial groups (µg/ml) | t test (df); p-values |
|--|-------------------------------------|--------------------------------|---|-----------------------|
| Erlotinib  | 1.45                                | 1.36                           | 0.09                                    | 0.244 (13); 0.81      |
| Sorafenib  | 5.48                                | 6.37                           | -0.89                                   | -0.530 (13); 0.60     |
| Sunitinib  | 0.082                               | 0.042                          | 0.04                                    | 1.512 (5); 0.19       |
| Average Z-scores of plasma determinations (standard deviation) | 0.065 (1.044)                       | -0.068 (0.913)                 | 0.13 (0.972)                            | 0.412 (35); 0.68      |

| Variables                   | Coefficient | Standard error | T-value | p-value |
|-----------------------------|-------------|----------------|---------|---------|
| Experimental group          | 0.40        | 0.169          | 2.423   | 0.016   |
| Toxicity                    | 0.11        | 0.03           | 4.116   | 0.001   |
| TCl-Reward Dependence Scale | 0.04        | 0.01           | 3.328   | 0.01    |
| Dose reduction (Yes/No)     | -0.38       | 0.176          | -2.142  | 0.033   |

**TABLE 3** Multivariate linear regression coefficients of variables on standardised plasma drug concentration, controlled by type of oral chemotherapy<sup>a</sup> (N = 37)

Note: F test = 6.137 on 6 and 146 df. Adjusted R-square = 0.20.

Abbreviation: TCl, Temperament and Character Inventory.

<sup>a</sup>Original values for the drug plasma concentration at each visit were used.

with respect to the standard of care, as received by the control group. Moreover, the EG patients reported a tendency to have lower levels of concern regarding treatment administration, side effects and efficacy.

It is known that medication adherence is influenced by various factors, which can depend on the patient himself, the disease state, the medication and the medical staff (Lima et al., 2018; Spoelstra et al., 2016). Indeed, previous studies have been conducted in order to determine preventive strategies and improve the percentage of medication adherence among patients undergoing oral therapy for prolonged periods (Krikorian et al., 2019; Medeiros et al., 2019; Ross et al., 2019; Spoelstra et al., 2016). In order to detect adherence with an objective measure, our study performed repeated and regular determinations of plasma drug levels during the visits. However, this method had a couple of drawbacks: the consideration of specialised staff and equipment and interpatient variability due to individual differences in absorption and metabolism (Ruddy et al., 2009).

Furthermore, the average toxicity total score of our EG patients significantly differed from that of the control group. A hypothetical interpretation of these data may refer to greater knowledge of the side effects as a result of the information provided by the hospital pharmacist. In turn, the EG patients may have had better awareness and more sensitivity in detecting and reporting such symptoms than the CG.

Regarding a psychological point of view, previous studies have only partially investigated the effect of patients' psychological characteristics on adherence (Leon et al., 2016; Reach, 2012). In addition to complete pharmacological information, it is necessary to investigate patients' individual characteristics, which can foster or reduce

therapy adherence, making it even more challenging. A couple of previous studies have detected a relationship between personality traits and treatment adherence (Lima et al., 2018; Tominaga et al., 2018). Other researchers have highlighted that high levels of neuroticism predict the use of maladaptive coping strategies, resulting in a poor adaptation to disease and catastrophising, both of which are known to be associated with the development and maintenance of chronic pain (Hirsh et al., 2008).

Oral chemotherapies require patients to take an active role in their health care; they must receive correct, professional health education on their disease and treatment (Goodridge et al., 2018). In this context, personality variables have a complex interaction with emotional distress, making it difficult to analyse them separately. Temperament is known to be stable across time and responsible for adaptive emotional responses and behavioural reactions to variations in an individual's environment. It also influences the subjective perception of situations and consequent reactions to them. Conversely, character is considered a learned personality component that can mature throughout a lifetime. Our results highlight the relevance of personality on treatment adherence, suggesting that people with a high level of the Reward Dependence trait are more likely to adhere to drug therapy. In fact, this trait relates to psychological and social attachment systems. Specifically, a high level of this trait implies a high attachment or dependence on external approval. Adherence to medication may indicate a propensity towards an "adherence attitude," with a tendency to be more obedient.

Taken together, these results allow us to hypothesise that a hospital pharmacist in combination with predisposing individual factors

(e.g. high level of the Reward Dependence personality trait) may have played a key role in adherence to chronic therapy, as measured at follow-up visits.

The procedures adopted in our study were similar to those applied by Simons et al. (2011). They studied the effect of an intensified pharmaceutical intervention on the adherence of cancer patients. A clinical pharmacist provided detailed information about drug management, possible side effects and the mechanism of action. In addition to spoken information, a leaflet was handed to the patients concerning the management and prevention strategy of side effects. The results showed that patients who were informed and supported by the pharmaceutical care consultations maintained an overall/daily adherence above 80% and a low grade of toxicity (Simons et al., 2011). Nevertheless, this study did not provide an objective measure for adherence; instead, it took an indirect approach, using an electronic medication event monitoring system.

Finally, while we observed only a trend towards better compliance in the objective outcome that was not statistically significant, the subjective measure, that is the patients' satisfaction with the RM, highlights the efficacy of reinforcement messages administered by the hospital pharmacist.

The present study has several limitations that should be considered. First, the sample size was relatively small. Second, our procedure involved a single RM performed by hospital pharmacists. A repetition of this intervention in follow-up visits would have likely increased adherence levels. Future multicentre studies with a larger sample should be conducted to confirm our results.

In conclusion, adequate information and education on a therapy, as provided by a hospital pharmacist, seems to positively influence treatment adherence. We can recommend introducing an RM strategy to the clinical standard care of patients undergoing oral treatment to maximise their adherence. Since this strategy implies a reasonable cost in terms of the required time to "reinforce" the patients, a significant benefit could be obtained in terms of patient satisfaction and medication adherence.

## CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

## ORCID

Lorys Castelli  <https://orcid.org/0000-0001-5009-2271>

## REFERENCES

- Awada, A., Hendlisz, A., Gil, T., Bartholomeus, S., Mano, M., de Valeriola, D., Strumberg, D., Brendel, E., Haase, C. G., Schwartz, B., & Piccart, M. (2005). Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumors. *British Journal of Cancer*, *92*(10), 1855–1861. <https://doi.org/10.1038/sj.bjc.6602584>
- Blanchet, B., Billemon, B., Cramard, J., Benichou, A. S., Chhun, S., Harcouet, L., Ropert, S., Dauphin, A., Goldwasser, F., & Tod, M. (2009). Validation of an HPLC-UV method for sorafenib determination in human plasma and application to cancer patients in routine clinical practice. *Journal of Pharmaceutical and Biomedical Analysis*, *49*(4), 1109–1114. <https://doi.org/10.1016/j.jpba.2009.02.008>
- Bouwman, L., Eeltink, C. M., Visser, O., Janssen, J. J. W. M., & Maaskant, J. M. (2017). Prevalence and associated factors of medication non-adherence in hematological-oncological patients in their home situation. *BMC Cancer*, *17*(1), 739. <https://doi.org/10.1186/s12885-017-3735-1>
- Britten, C. D., Kabbinavar, F., Hecht, J. R., Bello, C. L., Li, J., Baum, C., & Slamon, D. (2008). A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period. *Cancer Chemotherapy and Pharmacology*, *61*(3), 515–524. <https://doi.org/10.1007/s00280-007-0498-4>
- Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares? In *Mayo Clinic Proceedings* (Vol. 86, No. 4, pp. 304–314). Elsevier.
- Castelli, L., Binaschi, L., Caldera, P., & Torta, R. (2009). Depression in lung cancer patients: is the HADS an effective screening tool? *Supportive Care in Cancer*, *17*(8), 1129–1132. <https://doi.org/10.1007/s00520-009-0604-8>
- Cloninger, C. R., Przybeck, T. R., Svrakic, D. M., & Wetzel, R. D. (1994). *The Temperament and Character Inventory (TCI): A Guide to its Development and Use*. Center for Psychobiology of Personality, Washington University.
- Cramer, J. A., Roy, A., Burrell, A., Fairchild, C. J., Fuldeore, M. J., Ollendorf, D. A., & Wong, P. K. (2008). Medication compliance and persistence: terminology and definitions. *Value in Health*, *11*(1), 44–47. <https://doi.org/10.1111/j.1524-4733.2007.00213.x>
- Edwards, R. R., Giles, J., Bingham, C. O., Campbell, C., Haythornthwaite, J. A., & Bathon, J. (2010). Moderators of the negative effects of catastrophizing in arthritis. *Pain Medicine*, *11*, 591–599. <https://doi.org/10.1111/j.1526-4637.2010.00804.x>
- Etienne-Grimaldi, M. C., Renée, N., Izzedine, H., & Milano, G. (2009). A routine feasible HPLC analysis for the anti-angiogenic tyrosine kinase inhibitor, sunitinib, and its main metabolite, SU12662, in plasma. *Journal of Chromatography B*, *877*(29), 3757–3761. <https://doi.org/10.1016/j.jchromb.2009.09.011>
- Felton, M. A., van Londen, G. J., & Marcum, Z. A. (2016). Medication adherence to oral cancer therapy: the promising role of the pharmacist. *Journal of Oncology Pharmacy Practice*, *22*(2), 378–381. <https://doi.org/10.1177/1078155214559114>
- Fossati, A., Donati, D., Donini, M., Novella, L., Bagnato, M., & Maffei, C. (2001). Temperament, character, and attachment patterns in borderline personality disorder. *Journal of Personality Disorders*, *15*, 390–402. <https://doi.org/10.1521/pedi.15.5.390.19197>
- Gatwood, J., Gatwood, K., Gabre, E., & Alexander, M. (2017). Impact of clinical pharmacists in outpatient oncology practices: A review. *American Journal of Health-System Pharmacy*, *74*(19), 1549–1557. <https://doi.org/10.2146/ajhp160475>
- Goodridge, D., Henry, C., Watson, E., McDonald, M., New, L., Harrison, E. L., Scharf, M., Penz, E., Campbell, S., & Rotter, T. (2018). Structured approaches to promote patient and family engagement in treatment in acute care hospital settings: protocol for a systematic scoping review. *Systematic Reviews*, *7*(1), 35. <https://doi.org/10.1186/s13643-018-0694-9>
- Grassi, L., Buda, P., Cavana, L., Annunziata, M. A., Torta, R., & Varetto, A. (2005). Styles of coping with cancer: the Italian version of the Mini-Mental Adjustment to Cancer (Mini-MAC) scale. *Psychooncology*, *14*(2), 115–124. <https://doi.org/10.1002/pon.826>
- Hall, A. E., Paul, C., Bryant, J., Lynagh, M. C., Rowlings, P., Enjeti, A., & Small, H. (2016). To adhere or not to adhere: Rates and reasons of medication adherence in hematological cancer patients. *Critical Reviews in oncology/hematology*, *97*, 247–262. <https://doi.org/10.1016/j.critrevonc.2015.08.025>
- Haynes, R. B., Ackloo, E., Sahota, N., McDonald, H. P., & Yao, X. (2008). Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*, *16*(2), CD000011. <https://doi.org/10.1002/14651858.CD000011>

- Hidalgo, M., Siu, L. L., Nemunaitis, J., Rizzo, J., Hammond, L. A., Takimoto, C., Eckhardt, S. G., Tolcher, A., Britten, C. D., Denis, L., Ferrante, K., Von Hoff, D. D., Silberman, S., & Rowinsky, E. K. (2001). Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *Journal of Clinical Oncology*, *19*(13), 3267–3279. <https://doi.org/10.1200/JCO.2001.19.13.3267>
- Hirsh, A. T., George, S. Z., Bialosky, J. E., & Robinson, M. E. (2008). Fear of pain, pain catastrophizing, and acute pain perception: relative prediction and timing of assessment. *The Journal of Pain*, *9*(9), 806–812. <https://doi.org/10.1016/j.jpain.2008.03.012>
- Jerant, A., Chapman, B., Duberstein, P., Robbins, J., & Franks, P. (2011). Personality and medication non-adherence among older adults enrolled in a six-year trial. *British Journal of Health Psychology*, *16*, 151–169. <https://doi.org/10.1348/135910710X524219>
- Keating, G. M. (2017). Sorafenib: a review in hepatocellular carcinoma. *Targeted Oncology*, *12*(2), 243–253. <https://doi.org/10.1007/s11523-017-0484-7>
- Krikorian, S., Pories, S., Tataronis, G., Caughey, T., Chervinsky, K., Lotz, M., Shen, A. H., & Weissmann, L. (2019). Adherence to oral chemotherapy: Challenges and opportunities. *Journal of Oncology Pharmacy Practice*, *25*(7), 1590–1598. <https://doi.org/10.1177/1078155218800384>
- Leon, L., Redondo, M., Garcia-Vadillo, A., Perez-Nieto, M. A., Rodriguez-Rodriguez, L., Jover, J. A., Gonzalez-Alvaro, I., & Abasolo, L. (2016). Influence of patient personality in the treatment of rheumatoid arthritis. *Rheumatology International*, *36*(11), 1549–1555. <https://doi.org/10.1007/s00296-016-3561-9>
- Lima, M. P., Machado, W. L., & Irigaray, T. Q. (2018). Predictive factors of treatment adherence in cancer outpatients. *Psychooncology*, *27*(12), 2823–2828. <https://doi.org/10.1002/pon.4897>
- Measso, G., Cavarzeran, F., Zappalà, G., Lebowitz, B. D., Crook, T. H., Pirozzolo, F. J., Amaducci, L. A., Massari, D., & Grigoletto, F. (1993). The mini-mental state examination: Normative study of an Italian random sample. *Developmental Neuropsychology*, *9*(2), 77–85. <https://doi.org/10.1080/87565649109540545>
- Medeiros, K. S., Queiroz, J. F., Monteiro, M. N., Costa, W. A., Cobucci, R. N., Stransky, B., & Gonçalves, A. K. (2019). Impact of mobile applications on adherence to cancer treatment: a systematic review and meta-analysis protocol. *British Medical Journal Open*, *9*(11), e027246. <https://doi.org/10.1136/bmjopen-2018-027246>
- Mielke, P. W. Jr (1976). Simple iterative procedures for two-parameter gamma distribution maximum likelihood estimates. *Journal of Applied Meteorology*, *15*, 181–183. [https://doi.org/10.1175/1520-0450\(1976\)015<0181:SIPFTP>2.0.CO;2](https://doi.org/10.1175/1520-0450(1976)015<0181:SIPFTP>2.0.CO;2)
- Motzer, R. J., Hutson, T. E., Olsen, M. R., Hudes, G. R., Burke, J. M., Edenfield, W. J., Wilding, G., Agarwal, N., Thompson, J. A., Cella, D., Bello, A., Korytowsky, B., Yuan, J., Valota, O., Martell, B., Hariharan, S., & Figlin, R. A. (2012). Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. *Journal of Clinical Oncology*, *30*(12), 1371–1377. <https://doi.org/10.1200/JCO.2011.36.4133>
- Neuss, M. N., Polovich, M., McNiff, K., Esper, P., Gilmore, T. R., LeFebvre, K. B., Schulmeister, L., & Jacobson, J. O. (2013). 2013 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. *Journal of Oncology Practice*, *9*(2 Suppl), 5s–13s. <https://doi.org/10.1200/JOP.2013.000874>
- Reach, G. (2012). Two character traits associated with adherence to long term therapies. *Diabetes Research and Clinical Practice*, *98*(1), 19–25. <https://doi.org/10.1016/j.diabres.2012.06.008>
- Rosell, R., Carcereny, E., Gervais, R., Vergnenegre, A., Massuti, B., Felip, E., Palmero, R., Garcia-Gomez, R., Pallares, C., Sanchez, J. M., Porta, R., Cobo, M., Garrido, P., Longo, F., Moran, T., Insa, A., De Marinis, F., Corre, R., Bover, I., & Paz-Ares, L. (2012). Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncology*, *13*(3), 239–246. [https://doi.org/10.1016/S1473-2045\(11\)70393-X](https://doi.org/10.1016/S1473-2045(11)70393-X)
- Ross, X. S., Gunn, K. M., Patterson, P., & Olver, I. (2019). Development of a smartphone program to support adherence to oral chemotherapy in people with cancer. *Patient Preference and Adherence*, *13*, 2207. <https://doi.org/10.2147/PPA.S225175>
- Royston, J. P. (1982). An extension of Shapiro and Wilk's W test for normality to large samples. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, *31*(2), 115–124. <https://doi.org/10.2307/2347973>
- Ruddy, K., Mayer, E., & Partridge, A. (2009). Patient adherence and persistence with oral anticancer treatment. *CA: A Cancer Journal for Clinicians*, *59*(1), 56–66. <https://doi.org/10.3322/caac.20004>
- Sanii, Y., Torkamandi, H., Gholami, K., Hadavand, N., & Javadi, M. (2016). Role of pharmacist counseling in pharmacotherapy quality improvement. *Journal of Research in Pharmacy Practice*, *5*(2), 132–137. <https://doi.org/10.4103/2279-042X.179580>
- Simons, S., Ringsdorf, S., Braun, M., Mey, U. J., Schwindt, P. F., Ko, Y. D., Schmidt-Wolf, I., Kuhn, W., & Jaehde, U. (2011). Enhancing adherence to capecitabine chemotherapy by means of multidisciplinary pharmaceutical care. *Supportive Care in Cancer*, *19*(7), 1009–1018. <https://doi.org/10.1007/s00520-010-0927-5>
- Spoelstra, S. L., Burhenn, P. S., DeKoekkoek, T., & Schueller, M. (2016). A trial examining an advanced practice nurse intervention to promote medication adherence and symptom management in adult cancer patients prescribed oral anti-cancer agents: study protocol. *Journal of Advanced Nursing*, *72*(2), 409–420. <https://doi.org/10.1111/jan.12828>
- Tominaga, Y., Amori, T., Hayakawa, T., Kijima, N., Morisky, D. E., Takahashi, K., & Mochizuki, M. (2018). Possible associations of personality traits representing harm avoidance and self-directedness with medication adherence in Japanese patients with type 2 diabetes. *Journal of Pharmaceutical Health Care and Sciences*, *3*(4), 16. <https://doi.org/10.1186/s40780-018-0112-4>
- Zerillo, J. A., Goldenberg, B. A., Kotecha, R. R., Tewari, A. K., Jacobson, J. O., & Krzyzanowska, M. K. (2018). Interventions to improve oral chemotherapy safety and quality. *JAMA Oncology*, *4*(1), 105–117. <https://doi.org/10.1001/jamaoncol.2017.0625>
- Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370.