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Qualitative study of patients with metastatic prostate cancer to adherence of hormone therapy

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ABSTRACT

Purpose: To explore adherence to oral hormone treatment in patients with metastatic prostate cancer (mCRPC) and to identify the factors that influence it.

Methods: A qualitative exploratory study was conducted at the National Cancer Institute of Rome. Patients aged > 18 years with castration-resistant prostate cancer (mCRPC) and who were using oral hormone drugs were recruited. Semi-structured interviews were used for data collection, subsequently transcribed verbatim and analysed using Ritchie and Spencer's framework analysis.

Results: The sample included 13 patients with a median age of 72 who were treated, on average, for seven months with abiraterone acetate (AA) (76.9%) and enzalutamide (ENZ) (23.1%). Five themes were identified: expression of the concept of adherence, favouring factors, obstacle factors, functional strategies and levels of adherence.

Conclusions: The patients express a good level of adherence, which they define in different ways—the helping relationship with the attending physician, the support of the family members and the few side effects of the drugs. For the future, it is recommended to perform a multicentre mixed method study to explain the levels of adherence and distress in women with breast cancer.

1. Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer and is also the second leading cause of cancer-related death in men worldwide (Siegel et al., 2015). In the United States, there is an incidence rate of 1 in 7 cases (American Cancer Society, 2017) and a mortality rate of 1 in 39 men (US National Institutes of Health, 2013). In Europe, the incidence of PCa is higher in the northern and western areas, with more than 200 cases per 100,000 men per year (Mottet et al., 2017). This figure appears to be associated to exogenous factors, such as diet, chronic inflammation, sexual behaviour and low exposure to ultraviolet radiation (Mottet et al., 2017). In Italy, it represents 20% of all cancers diagnosed from age 50, with an incidence of 34,800 new cases and 7174 deaths per year (Aiom-Airtum, 2016).

In consideration of these epidemiological data, over time it has become an important public health problem (Lange et al., 2017). Because it can present itself in different forms, the personalization of care represents the most serious challenge in the treatment of this pathology. The choice of treatment depends on several factors, including the histological and molecular characteristics of the tumour and the characteristics of the patient (stage, degree and size of the tumour and age), which can influence the clinical history of the disease and the patient's response to therapies. The therapeutic strategies available today consist of loco-regional treatments (surgery, radiotherapy and brachytherapy) and general treatments (chemotherapy and endocrine therapy). After primary treatment utilizing chemical castration and/or radiotherapy or surgery, most patients progress to a state of the disease called castration-resistant prostate cancer (CRPC) (Behl et al., 2017). This condition is associated with a survival of about two years, a constant increase in prostate antigen (PSA) in serum levels and the appearance of metastases (mCRPC) (Saad and Hotte, 2010). In recent years, treatment options for this type of cancer have expanded thanks to

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the use of new drugs, such as docetaxel, cabazitaxel, abiraterone acetate (AA), enzalutamide (ENZ) and radium 223 (De Bono et al., 2011; Parker et al., 2013; Ryan et al., 2013; Beer et al., 2014; Recine et al., 2015; Behl et al., 2017).

Among these, in particular, the introduction of AA and ENZ (Heidenreich et al., 2014) has revolutionized the management of mCRPC. AA is an androgen biosynthesis inhibitor approved by the US Food and Drug Administration (FDA) in 2011 for use in combination with prednisone (synthetic corticosteroid usually taken orally) as a treatment for patients with mCRPC before and after previous treatment with docetaxel (Ang et al., 2009; De Bono et al., 2011; Ryan et al., 2013; Behl et al., 2017). ENZ acts by blocking the signal transduction at the androgen receptor level, and was approved by the FDA for the treatment of mCRPC in 2012, also in the same patient setting, before and after treatment with docetaxel (Scher et al., 2012; Beer et al., 2014; Behl et al., 2017). Thanks to their wide use and tolerability, these drugs, both administered once a day in a fixed oral dose, have acquired great importance in recent years, especially as an advanced therapy (FDA, 2012, 2015; Committee for Medicinal Products for Human Use, 2013).

This success is also linked to the fact that the availability of anticancer treatments in oral form aligns with patients' preferences, can help improve their quality of life and reduces the amount of time spent in healthcare facilities; however, with the availability and use of oral formulations comes the problem of adherence (Sabaté, 2003).

Adherence is defined as self-management in agreement with specific instructions (Haynes et al., 2008), the coincidence of actions or behaviors with advice or instructions (Christensen, 2004), the cooperation, with a collaborative an voluntary relationship (Chisholm et al., 2000), to achieve the acceptable objectives (Rose et al., 2000).

The latter is now considered a key element of the therapy and one of the most important problems in clinical practice since it depends on the success of any intervention; in fact, non-adherence leads to a reduction in disease-free survival, treatment efficacy, an increase in the number and duration of hospitalizations and the progression of the disease (Makubate et al., 2013).

The literature reports a wide range of factors that can affect adherence, categorized by the World Health Organization (WHO) as socioeconomic factors, patient-related factors (forgetfulness, denial of disease, religious belief and poor understanding of therapy), factors related to the clinical condition (symptoms not apparent or very mild or even very severe and state of confusion), factors related to the health system and the team of health professionals and factors related to the prescribed therapy (difficult preparation, complex regimen, high frequency of intake, undesirable effects and adverse reactions to drugs) (Sabaté, 2003).

Adherence estimates for patients taking oral antineoplastic medication range from less than 20%–100%, but are typically between 50% and 90% (Geynisman and Wickersham, 2013; Spoelstra et al., 2013; Bassan et al., 2014; Greer et al., 2016). In particular, adherence to oral hormone treatment in patients with mCRPC has, to date, has been rarely investigated, and the few studies conducted are quantitative in nature. In a study conducted by Lafeuille et al. (2014), a level of adherence to AA was observed, measured with the medication possession ratio (MPR) at over 90%, while in a Smith et al. study (2015), six months after starting treatment, only 83.0% of patients had an MPR over 80.0%.

However, to understanding adherence to treatment, it is necessary to consider experience as well as the patient's point of view in order to make a contribution to this phenomenon. As qualitative studies are not currently available in the literature the aim of this study is to explore the phenomenon of adherence to oral hormone treatment in patients with mCRPC and the factors that may influence their adherence.

2. Methods

This qualitative exploratory study was carried out at the IRCCS "Regina Elena" National Cancer Institute in Rome. Patients were recruited on follow-up visits on Monday and Wednesday for prostate disease, if they were over the age of 18, had a diagnosis of mCRPC and were being treated with oral hormone therapy (AA or ENZ). Exclusion criteria were the presence of cognitive deficits or pathological conditions that could be an obstacle to the active participation in the interviews. Sampling was purposeful (Streubert and Carpenter, 2011) in order to solicit rich personal experience of the phenomenon under study. The sample size of patients for the qualitative study was defined by the data saturation principle (Streubert and Carpenter, 2011). The data can be considered complete when the dominant themes are recurrent and no others have emerged from new collection (Stebbins, 2001; Liamputtong, 2010).

Table 1
Interview guide questions.

1 What oral therapy do you take?
2 What does it mean for you to 'adhere' to medication?
3 Have you always taken the medicine?
If yes:
What facilitated the assumption? What could prevent it?
If no:
What has prevented your hiring? What could help it?
4 What is your experience of taking oral hormonal therapy?
5 What can you suggest to improve adherence to drug administration?

A semi-structured interview was conducted to investigate the significance that patients attribute to the adherence phenomenon, the experience of taking drugs and factors that contribute or hinder the normal intake of medication. This interview was guided by a series of questions (Table 1), which were designed to facilitate and encourage the person to speak and give voice to the subjective part of this experience, while appreciating various nuances and allowing participants the opportunity to respond openly and spontaneously expand on their answers.

Before the start of the study, approval from the Ethical Committee of the I.F.O. Istituti Fisioterapici Ospitalieri of Rome was obtained (Prot. N. 709/15 of 15.09.2015). Patients, whose characteristics met the inclusion criteria of the present study, were apprised of the objectives of the survey and the modalities of the interview and were asked to read the informed consent document carefully before making the choice to participate.

All interviews were completely audio recorded, transcribed word for word and analysed using the framework analysis with a contextual approach (Spencer and Ritchie, 2002; Ritchie et al., 2013). Each interview was read several times independently by two researchers (familiarization); then, when units of meaning had been identified, we defined the codes and their categories for subsequent comparisons and abstractions (indexing). Through a discussion with three other researchers, the categories were combined by similarity of meaning to form themes (charting) that summarize the essential concepts of the participants' lives. Characters were used to map the themes of the phenomenon (mapping and interpretation) (Table 2).

3. Results

The sample is composed of 13 patients with a median age of 72 years (range: 66–83 years), mainly with an upper secondary school education (38.5%), married (76.9%), with children (76.9%) and having the status of a pensioner (92.3%) (Table 3).

The majority of patients were previously treated with chemotherapy (92.3%), radiotherapy (69.2%) and radical surgery (61.5%) (Table 4). A total of 76.9% of the sample at the time of the interview had been treated with AA while 23.1% had been treated with ENZ, on average, for seven months (range: 2–28 months) (Table 3).

The interviews lasted from 9 to 16 min. Topics that emerged from the analysis and the most significant phrases associated with them are

Table 2
Example of the coding process in inductive analysis. This matrix was used for each interview. This extract refers to the first emerged theme.

n. Interview	n. Page	Codes	Category	Theme
4	2	I am a soldier so if I have one thing I must do it!	Obligation/Duty	*Expression of the concept of adherence*
5	1	They told me that I had to do it because I had already done two cycles of chemotherapy and could not always be done; I take it because I have to do it …		
6	1	I know I have to take the tablets, I take the tablets, in short … just stop!		
13	2	I have to take it because I cannot do interference with the doctor …		
9	1	It's duty.		
5	1	I have seen this usefulness because the PSA has fallen and is better than other interventions	Utility/Clinical benefit	
8	2	It's a change of therapy to improve my condition …		
3	1	I take it like all the medicines is not that I make a difference between this that concerns the tumor and those that serve for the flu; it is the same for me as other medicines, and they give me maybe even less problems than the other medicines, so with this therapy I live normally	Habit	
7	2	These tablets are like other medicines		
11	1	It's an automatic gesture		

Table 3
Socio-demographic data.

n.	Age	Education	Marital Status	Work Status	Sons
1	72	Upper secondary school	Married	Pensioner	Yes
2	70	Upper secondary school	Married	Pensioner	Yes
3	74	Bachelor's degree	Widower	Pensioner	No
4	83	Lower secondary school	Widower	Pensioner	Yes
5	76	Master's degree	Married	Pensioner	Yes
6	66	Lower secondary school	Married	Pensioner	Yes
7	72	Upper secondary school	Married	Pensioner	Yes
8	66	Lower secondary school	Married	Merchant	Yes
9	78	Bachelor's degree	Married	Pensioner	No
10	75	Upper secondary school	Married	Pensioner	Yes
11	67	Bachelor's degree	Married	Pensioner	Yes
12	74	Bachelor's degree	Widower	Pensioner	No
13	72	Upper secondary school	Married	Pensioner	Yes

Table 4
Clinical data.

n.	Previous Radical Surgery	Previous Chemotherapy	Previous Radiotherapy	Hormonal Therapy	Time (months)
1	No	Yes	Yes	AA	4
2	Yes	Yes	Yes	AA	5
3	No	Yes	Yes	AA	6
4	No	Yes	Yes	AA	1
5	Yes	Yes	Yes	AA	2
6	Yes	Yes	Yes	AA	28
7	Yes	Yes	No	ENZ	5
8	Yes	Yes	No	AA	2
9	Yes	No	Yes	ENZ	12
10	Yes	Yes	No	ENZ	12
11	Yes	Yes	No	AA	12
12	No	Yes	Yes	AA	6
13	No	Yes	Yes	AA	4

AA: abiraterone acetate – ENZ: enzalutamide.

examined next.

3.1. Expression of the concept of adherence

This is the theme in which patients express their way of understanding the phenomenon related to the intake of drugs. Most patients reveal adherence as a total observance of medical indications, an obligation or duty, such as ‘ … I am a soldier so if I have one thing I must do it!’ (Interview No. 4, age: 83 years); ‘They told me that I had to do it because I had already done two cycles of chemotherapy and could not always be done; I take it because I have to do it … ’ (Interview No. 5, age: 76 years); ‘I know I have to take the tablets, I take the tablets, in short … just stop!’ (Interview No. 6, age: 66 years); and ‘I have to take it because I cannot do interference with the doctor … ’ (Interview No. 13, age: 72 years). Some patients, on the other hand, consider adherence in terms of utility: ‘I have seen this usefulness because the PSA has fallen and is better than other interventions’ (Interview No. 5, age: 76 years), and of its clinical benefit: ‘It's a change of therapy to improve my condition … ’ (Interview No. 8, age: 66 years). Others, however, speak of it in terms of a habit, equating the antineoplastic treatment with any other treatments: ‘I take it like all the medicines is not that I make a difference between this that concerns the tumour and those that serve for the flu; it is the same for me as other medicines, and they give me maybe even less problems than the other medicines, so with this therapy I live normally’. (Interview No. 3, age: 74 years).

3.2. Favouring factors

This is the theme in which patients clearly express what the aspects related to treatment are, among which mainly emerged the absence of side effects: ‘It did not give me any trouble!’ (Interview No. 4, age: 83 years); ‘Does not give me side effects so I prefer it over other types of treatment’ (Interview No. 11, age: 67 years); the composition of the pills: ‘It's really very simple … even the pills are relatively small’. (Interview No. 9, age: 78 years); the preference over the chemotherapy: ‘The alternative was chemotherapy. I was offered this treatment that I think is more bearable because the chemotherapy would have been very different’. (Interview No. 2, age: 70 years); ‘So I prefer this oral because in the meantime. I do it at home and I manage it well, because with chemotherapy I had to come here, get up early, and … ’. (Interview No. 4, age: 83 years); the completeness of the information received on the treatment: ‘All the doctor told me … and it was also very clear when he explained them to me’. (Interview No. 5, age: 76 years); ‘The doctor … he was the one to advise me and also gave me a leaflet with all the indications’. (Interview No. 12, age: 74 years); and, finally, support of family members: ‘ … I have my wife, who calls me when I'm out, to remind me’. (Interview No. 2, age: 70 years); ‘It gives me the help of my wife and my family’. (Interview No. 13, age: 72 years).

3.3. Obstructive factors

This is the theme in which patients express the aspects related to the treatment, from a physical point of view: ‘There is the problem of chemical castration … ’ (Interview No. 1, age: 72 years); ‘ … I cannot walk and, oh well, when I cannot I sit somewhere and wait, because I really care about traveling’. (Interview No. 3, age: 74 years); in terms of psychological effects: ‘ … more than anything else is the psychological discomfort because I do not see the improvements and then I say “Why I must to take it?” … but it is not that I am a slave to something or obsessed is because you lose confidence in the positive effect of the product’. (Interview No. 3, age: 74 years); concerning the management of the polytherapies: ‘Look at the fact that there are four, because I

swallow two at a time, and at my age maybe I'm in front of the TV while I swallow and then I think “but did I take the first two or all the pills?” And this seems trivial but in the morning, one is sleepy, wakes up and does this operation. It can happen, this problem can occur, then if it were a single tablet one takes it and swallows it’. (Interview No. 1, age: 72 years); about the size of the treatment: ‘ … it's a sacrifice to swallow 4 tablets big enough!’ (Interview No. 8, age: 66 years); and the supply of the medicine: ‘Every month I have to come here to take these tablets … try to give instead of one, at least two boxes, to reduce the frequency of access to hospital […] and if I have to take the therapy for life and one day I cannot come, how can I?’ (Interview No. 7, age: 72 years).

3.4. Functional strategies

This is the theme that highlights the set of functional strategies that the patient uses to take the treatment, including: the ability to self-manage the treatment as evidenced by the following statements: ‘ … I do it all by myself because I have my own autonomy, my mind is still there, I'm fine’. (Interview No. 4, age: 83 years); to use motivational drives: ‘ … I have to go forward, as they say in these cases, in the best way!’ (Interview No. 2, age: 70 years); and resorting to types of reminders: ‘ … I can organize myself because I set the alarm’. (Interview No. 1, age: 72 years); ‘I have a little box that I always carry with me … ’ (Interview No. 12, age: 74 years).

3.5. Adherence levels

In this theme, patients define their level of adherence. All report optimal and constant intake over time: ‘ … if anything, I have postponed a few hours, but I have always taken it’. (Interview No. 3, age: 74 years); ‘ … I take great care of it … I always take it!’ (Interview No. 4, age: 83 years); ‘I've always got it … ’ (Interview No. 5, age: 76 years), ‘absolutely … I've always taken them’. (Interview No. 11, age: 67 years); with an oversight, sometimes, linked to an exceptional event, such as a trip: ‘ … maybe here is an extraordinary event that maybe I leave and I forget’. (Interview No. 1, age: 72 years); ‘Yes, I have always taken them, except on one day while coming from Abruzzo to Rome for the visit … (Interview No. 2, age: 70 years).

4. Discussion

The objective of this study was to explore the phenomenon of adherence to oral hormone treatment in patients with mCRPC and the factors that may influence it.

The introduction of oral antineoplastic therapies (O’neill and Twelves, 2002; Findlay et al., 2007; Greer et al., 2016) has induced a ‘responsibility’ that, although optimal for many subjects, may be overwhelming for others (Barillet et al., 2015), making adherence an important parameter in reducing the risk of treatment failure.

From the interviews, it emerged that patients give different meanings to the concept of adherence. One person considers the therapy to be taken in terms of adherence, including acceptance and awareness, and this concept includes an understanding of the actual clinical benefit of the treatment. Other patients understand it in terms of compliance, or as an obligation/duty to faithfully take the prescriptions from the medical oncologist. The different meanings of the concept of adherence are related to the different modalities of defining this term in the scientific literature, that is, as an interchangeable synonym for compliance, concordance, obedience, observance, conformity, acceptance, cooperation, mutuality and therapeutic alliance (Bissonette, 2008), as an observance of specific instructions (Haynes et al., 2005), a coincidence of behaviours with advice or instructions (Christensen, 2004), a collaboration to achieve acceptable objectives (Rose et al., 2000) and as a voluntary collaborative relationship (Chisholm et al., 2000).

Our study showed that patients, despite having a medium-high age, expressed a good level of adherence to hormonal treatment, although the literature reported lower adherence rates in older patients (Sabaté, 2003; Nabid et al., 2012).

Regarding the factors favouring the treatment, it has emerged that antineoplastic oral treatment is preferred by patients compared to intravenous chemotherapy, since it is less invasive and because it can be taken in the comfort of one's home (Neuss et al., 2013).

Even the lack of side effects in our sample, most likely linked to the short period of time from the beginning of the drug intake, has certainly influenced adherence to the treatment; this result coincides with the scientific literature which states that adverse events do not only limit the quality of life of patients, but also contribute significantly to the interruption of treatment (Holle et al., 2016).

Moreover, the assumption can also be justified by the good level of information on the management of the therapy that the patients received from the doctor during outpatient visits, which they report in the interviews with great conviction and certainty. The relationship established with the treating oncologist, to which more than one patient refers, reporting the name and surname in interviews, emphasizes the existence of an optimal helping relationship. Adherence, in fact, requires a particular attention to the person, or an approach focused on providing personalized assistance, which guarantees therapeutic communication, continuity of care, direct contact with staff and the activation of functional self-care strategies (Holmes and Lenz, 1997; DiMatteo, 2004; Palmieri and Barton, 2007; Miaskowski et al., 2008; Iacorossi et al., 2018). In fact, the patients interviewed, thanks to the information they received, have also put into place different ways to remember the assumption of the drug, including the use of alarms and reminders such as by placing the box in view or in their pocket. This information, which is linked to the advanced stage of the pathology in which the patients are found, has also provided a motivational boost by considering the drug ‘useful’ both on the controls and on the possible comparison/lengthening/changing of therapy. This index of patients' decision-making balance is consistent with the work of Horne and Weinman (1999), which states that adherence to therapy is observed when the clinical benefits outweigh the risks (cost-benefit analysis).

Another important factor favouring the treatment of patients in our study is the support of family members, particularly wives, both as a psychological support and as a reminder, even if, in our case, the forgetfulness was only in two patients and linked to an exceptional event such as a trip. This data is confirmed by the literature according to which having a family/social support (Sabaté, 2003) and being married (Iacorossi et al., 2016), promote adherence to treatment.

Data on unfavourable factors affecting adherence in our study were polytherapy, drug size and procurement. The literature reports that treatment patterns requiring two or more daily doses are associated with lower adherence compared to those with a single daily dose (Claxton et al., 2001). Patients with multiple therapeutic regimens face further challenges in dosage and administration. Despite this, in the study, very few patients complained of difficulties related to the polytherapy, most likely related to the possible presence of co-morbidity, given the medium-high age of the sample recruited. Regarding the treatment, a different perception about the size of the drug was described: one patient complained about the large size; however, another noted that the small size had simplified the intake. These perceptions are part of what Hadji (2010) defines as predictors of non-adherence related to the patient and, in particular, to his beliefs about the composition of the drug.

A patient also complained of difficulties related to the periodic trips required to obtain the drug from the hospital, confirming supply as a possible predictor of non-adherence to treatment (Sabaté, 2003).

5. Conclusions

The objective of this study was to explore the phenomenon of adherence to oral hormone treatment in patients with mCRPC and the factors that may influence it. The Results show that patients expressed

an optimal level of adherence, which resulted from the extensive, easily understandable information received from the healthcare staff, the support of the family members as a presence and as a reminder and the few side effects related to treatment.

To make the Results generalizable, it is necessary to carry out a quantitative multicenter study to objectify and extend the adherence measurement. Also, this could be followed by a mixed method study to explain the levels of adherence and distress in women with breast cancer.

Conflicts of interest

The authors have no funding or conflicts of interest to disclose regarding this work.

CRediT authorship contribution statement

Laura Iacorossi: Data curation, Writing – original draft. **Francesca Gambalunga:** Data curation, Writing – original draft. **Rosaria De Domenico:** Data curation. **Valeria Serra:** Data curation. **Cristina Marzo:** Data curation. **Paolo Carlini:** Writing – original draft.

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