

Patients' perceived tolerance of side effects in phase I cancer clinical trials: A qualitative study

A. Brédart PhD, Psychologist^{1,2} | S. Bodson MA, Psychologist² | C. Le Tourneau MD, Medical Oncologist^{3,4} | C. Flahault PhD, Psychologist^{1,2} | F. Bonnetain PhD, Biostatistician⁵ | A. Beaudeau MA, Psychologist¹ | E. Coquan MD, Medical Oncologist^{3,4} | S. Dolbeault MD, Psychiatrist^{1,6} | X. Paoletti PhD, Biostatistician⁷

¹Psycho-Oncology Unit, Institut Curie, Paris, France

²Psychopathology and Health Process Laboratory (EA 4057), Psychology Institute, University Paris Descartes, Boulogne-Billancourt, France

³Department of Medical Oncology, Institut Curie, Paris & Saint-Cloud, France

⁴EA7285, Versailles-Saint-Quentin-en-Yvelines University, Montigny-le Bretonneux, France

⁵Methodology and Quality of Life in Oncology Unit (EA 3181) & Quality of Life and Cancer Clinical Research Platform, CHU Besançon, France

⁶Inserm, U 669, Paris, France

⁷Gustave Roussy Cancer Campus, Villejuif, France

Correspondence

A. Brédart, Psycho-Oncology Unit, Institut Curie, Paris, France.
Email: anne.bredart@curie.fr

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This qualitative study aimed to explore cancer patients' perceived tolerance of side effects in phase I drug trials. Patients with solid tumours receiving molecularly targeted agents with/without chemotherapy were eligible for inclusion. In-depth semi-structured interviews were carried out with 17 patients with a median [range] age of 63 [41–72] years. Treatment was discontinued in seven patients. Verbatim transcripts of the audio-taped interviews were analysed using a constructivist grounded theory approach. Four conceptual categories emerged from data analysis, labelled “suffering from side effects” comprising a range of symptoms, psychosocial or role disturbances; “striving to cope with side effects” reflecting psychological strategies for managing side effects; “hoping” reflecting expectations about treatment efficacy and relief from side effects; and “appraisal of care.” Among patients remaining in the trial, treatment was currently perceived as fairly tolerable. For most respondents, whether still in a trial or not, treatment discontinuation could not be justified by the non-tolerance of treatment side effects. These results question the adequacy of patient-perceived tolerance reports to determine an optimal drug dose for phase II trials. Confronted with patients' hopes and inappropriate beliefs, communication is challenging in phase I trials and could benefit from facilitating psychosocial interventions.

KEYWORDS

health-related quality of life, molecular targeted agents, patients' subjective experiences, phase I clinical trial, qualitative study, treatment tolerance

1 | INTRODUCTION

The main objective of phase I clinical trials is to identify the toxicity profile and define the optimal dose of a drug or a drug combination for further development in phase II and/or III trials (Paoletti et al., 2014). The typical population included in phase I clinical trials will have any solid tumour type that is refractory to all standard treatments. They have good vital functions but limited life expectancy.

An adverse event is any unfavourable and unintended sign or symptom associated with the use of a medical treatment or procedure (Barry

& Dancey, 2005). Adverse events are reported using the “National Cancer Institute - Common Toxicity Criteria for Adverse Events” (NCI CTCAE) on a grading scale ranging from 1 (*mild toxicity*) to 5 (*toxic death*). The fundamental assumption in oncology is that the maximum tolerated treatment dose (MTD) provides the optimal clinical efficacy associated with an acceptable toxicity profile (Postel-Vinay et al., 2011). Formally, the MTD is usually defined as the highest dose associated with less than 33% of severe toxicity (grade 3 or 4 according to the NCI CTCAE).

The validity of this paradigm, which was established at the time of cytotoxic chemotherapies, is debated for the molecularly targeted

agents (MTAs), which have been the focus of medical research over the past 20 years. MTAs block the growth and spread of cancer by interfering with specific mechanisms involved in tumour growth and progression (Gerber, 2008). Compared with cytotoxic drugs, they present lower toxicities and different toxicity profiles (e.g. diarrhoea and oedema) (Sodergren et al., 2014). The dose–efficacy positive relationship observed with cytotoxic agents is not always true with MTAs (Postel-Vinay, 2015). Besides, most MTAs are designed to be administered over long periods (typically until disease progression). While mild or moderate (grade 1 or 2 according to the NCI CTC-AE), the side effects may be long-lasting and may, therefore, specifically affect the tolerability of the agent (Paoletti et al., 2014).

New MTAs are being developed and tested in phase I trial protocols. Phase I research is designed as a dose-escalation trial that starts with a drug dose level that has little chance of producing an adverse event; if no severe toxicity occurs in a small group of 1–3 patients, doses are then sequentially escalated until the MTD is determined. Although the MTD definition is currently based exclusively the severity of toxicity observed after 3–6 weeks of treatment, criteria that can be considered to define the MTD include the toxicity grade level, the duration of the side effects, their occurrence at baseline, the need for drug dose modification, or for treatment postponement or discontinuation (Le Tourneau et al., 2011).

The MTD can be determined from the patient's symptoms (e.g. diarrhoea) or signs (e.g. thrombocytopenia) or the pharmacokinetic and pharmacodynamic properties of the agent being studied (Barofsky, 2012). Hence, both subjective and objective criteria are used to assess toxicity levels and adverse events. These are reported by clinicians on the basis of laboratory reports, clinical measures or observations. Whereas a number of toxicity signs (e.g. retinal tear) can be directly observed by clinical staff, symptoms such as pain, neuropathy, mood depression or fatigue are reported indirectly, inferred by the clinician on the basis of his/her observations or on the information volunteered by the patient (Atherton et al., 2015; Osoba, 2011).

Several studies showed that clinicians' assessments often underestimate the frequency and severity of certain toxic effects compared with patient reports, while the two can have complementary predictive value for health status (Basch et al., 2009; Di Maio et al., 2015; Fromme, Eilers, Mori, Hsieh, & Beer, 2004; Novello et al., 2014; Quinten et al., 2011). This led to consideration of patient-reported outcomes (PROs) to complement clinical outcomes in the evaluation of treatments. A PRO is defined as "any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy" (Patrick et al., 2007). Recently, Basch et al. (2014) developed a PRO measurement system as a companion to the CTC-AE, called the PRO-CTCAE. Patient-reported toxicities are appraised in terms of frequency, severity and interference with daily life.

It has been argued that patient-perceived symptoms and HRQL could be important markers of MTAs tolerability (Cella, 2011; Efficace et al., 2012). However, there is little direct information on the degree to which patients are able to tolerate any given treatment side effect

(Eton, Yost, & Cella, 2006) and will agree to pursue treatment, would define their perceived drug tolerance threshold nor on how they deal with the treatment side effects they are experiencing (Clough-Gorr, Stuck, Thwin, & Silliman, 2007).

Phase I clinical trials aim to determine a drug dose producing therapeutic effects, but this also increase the likelihood of producing side effects, resulting in adverse impacts on the patient's functioning and overall quality of life. Thus, investigating patients' experience of their qualitative health status in this context appears particularly relevant (Barofsky, 2012).

The purpose of this qualitative study was to describe patient-perceived side effect "tolerance" or "non-tolerance" in phase I trials on treatment using MTAs with/without chemotherapy, in terms of symptoms, functioning and treatment satisfaction, and to explore factors motivating any desire to discontinue treatment.

Ethical approval for the study was granted by the CCTIRS (Comité consultatif sur le traitement de l'information en matière de recherche scientifique) (approval no 13549). Patients were provided with a document describing the study and including contact details. The informed consent stated the possibility to withdraw and decline participation. Participants were asked for their agreement that the interview be audio-taped and the verbatim transcribed. They were assured that their words would be confidential and would not affect their care.

2 | METHODS

2.1 | Design

Patients were approached over the period between December 2013 and March 2014. Theoretical sampling (i.e. sampling for theory construction) (Strauss & Corbin, 1998) was used to maximise variation within the sample across age ranges and treatment status (defined as whether or not a decision was made to discontinue treatment). Patients enrolled in a phase I clinical trial and patients who had discontinued participation in one of these trials were included. So we gathered data from both speculative and retrospective perspectives on the extent to which a phase I MTAs with/without chemotherapy would be or was perceived as non-tolerable to the point that the patient would want to discontinue it.

Sample size was based on data saturation. At the data saturation point, no new additional material seems to emerge from the analysis (Guest, Bunce, & Johnson, 2006; Strauss & Corbin, 1998).

2.2 | Participants

The population was defined as any adult (i.e. aged 18 years or over) undergoing the second treatment cycle at least in a phase I clinical trial investigating one MTA, alone, or in combination with another MTA or chemotherapy, so that they had been exposed to treatment for at least 6 weeks. Patients were excluded if they had a malignant haematological disease or were participating in a phase I trial investigating radiotherapy (since adverse events may occur after a relatively long time lapse), hormone therapy or biological therapies such as gene

therapy (since they display completely different action mechanisms and toxicity profiles). The other exclusion criteria included inadequate fluency in French, psychiatric disorder and inadequate cognitive ability to provide informed consent.

2.3 | Procedure

Participants were identified and recruited during a visit to the clinical research unit in the Institut Curie (Paris). They were introduced to the study objectives and terms of participation. After informed consent was obtained, they were invited to take part in a face-to-face interview.

Interviews were conducted by the second author (SB) using open-ended questions to avoid leading the interview content and thus potentially introducing bias (Bredart, Marrel, Abetz-Webb, Lasch, & Acquadro, 2014). A semi-structured interview guide was designed prior to the study, refined after two pilot interviews, and then further developed throughout the analysis process (Figure 1). Patients were encouraged to talk about any change in symptoms or functioning since entering the clinical trial and to express their thoughts and feelings on their experience of side effects, whether they would assess the treatment as easy or difficult to tolerate, and what would lead them to want to discontinue treatment. Additional prompts covered treatment (dis)satisfaction (Abetz et al., 2005).

Socio-demographic (age and gender) and clinical data (type of primary cancer, time since cancer diagnosis, type of previous cancer treatment, and number of current clinical trial cycles received) were collected from patients' medical records after the interviews.

2.4 | Analysis

The transcripts were analysed on the basis of constructivist grounded theory (Charmaz, 2006). This approach has been described as a relevant qualitative method to capture a comprehensive representation

of subjects' experiences, feelings or thoughts on a phenomenon (Breckenridge, Jones, Elliott, & Nicol, 2012).

All transcripts were analysed, applying a line-by-line initial coding, i.e. labelling of themes (actions or events), followed by a focused coding which synthesised large amounts of data by using the initial codes that made the best analytic sense and categorised data the most accurately and completely (Charmaz, 2006). Focused codes that were similar were then grouped from all transcripts and allocated to more abstract conceptual categories using memos in which any spontaneous thoughts were noted about the content of the interviews. These categories were defined and their properties specified, along with conditions of emergence and consequences, and they were related to the other categories. Initial coding began at completion of the first interviews to enable relevant themes to be integrated into subsequent themes. The constant comparison method was used to enable comparisons of interview statements (or codes) within and across interviews. A thematic framework was inductively and incrementally formed in an iterative process consisting in further analysis and integrating new data.

The first three transcripts were double-coded blind by three authors (AB, SB, and CF). Coding discrepancies were discussed among researchers until an agreement on the semantic definition of the code was reached. Half of the remaining transcripts were coded by either AB or SB and further discussed. Feedback on the relevance of emerging results was solicited from other authors at three subsequent points of the analysis process.

Across themes, perusal of the interviews of patients who remained on treatment and those for whom treatment was discontinued evidenced similarities and differences. Illustrative excerpts from patient reports are provided for each group. These have been translated from French into English by an English-speaking translator to provide information on content, attempting to preserve the tone of remarks (quotations are labelled by patient number; patients who had discontinued treatment were encountered at a phase I trial follow-up medical consultation and are referred to as FU).

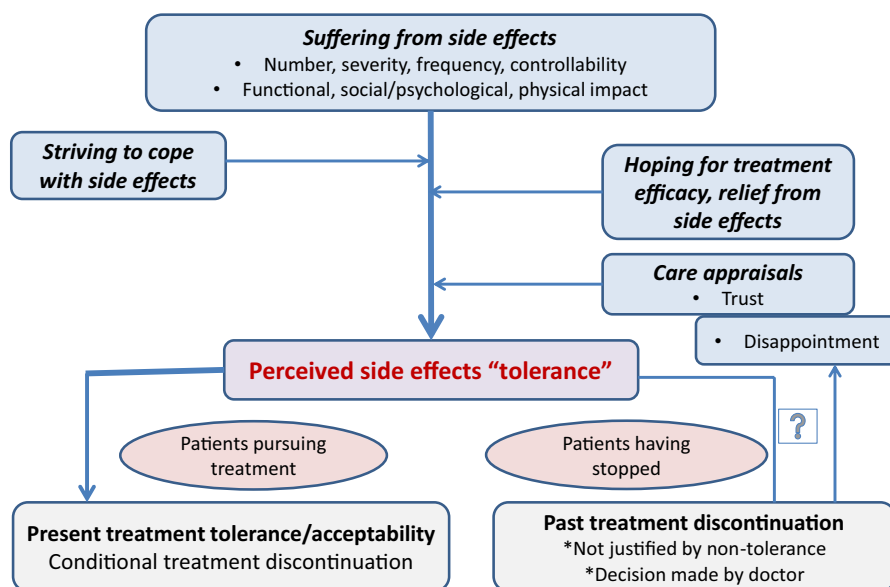


FIGURE 1 Relationships among factors of perceived tolerance in phase I MTAs with/without chemotherapy

3 | RESULTS

In all, 25 patients were approached, among whom six patients did not agree to participate in the study (three patients because they were not interested, two patients felt—and were reported to be—anxious or weary, and one patient was feeling unwell and reported poor health). Two interviews were considered pilot interviews. The mean (SD) duration of the interviews was 30 (± 15) min.

The main socio-demographic and clinical characteristics of the study participants ($N = 17$) and non-participants ($N = 6$) are described in Table 1.

Among participants, five were men and the median [range] age was 63 [41–72] years. Cancer diagnoses included choroid melanoma (eight patients), breast cancer (5), nasopharyngeal cancer (1), cervical cancer (2) and endometrial cancer (1) for which the trial agents were, respectively, oral protein kinase-C inhibitor, trastuzumab and emtansine in addition to capecitabine, demethylating agent, bispecific anti-VEGF/anti-ANG-2 antibodies, monoclonal antibody targeting CSF1r, paclitaxel and AKT inhibitor, and PD1 inhibitor or progesterone antagonist. Treatment discontinuation had been decided for seven patients at the time of interview.

3.1 | Perceived tolerance of side effects

Patients enrolled in a phase I trial did not report that their treatment or side effects were currently not tolerable or unacceptable. We had to explore the experience of “non-tolerance” of treatment or side effects either retrospectively, assessing their past cancer treatment (or trial discontinuation, in patients who had stopped the phase I experimental treatment), or speculatively, asking what would be felt as intolerable.

When asked about which side effects or which characteristics of these side effects had been or would be experienced as intolerable or difficult to bear, patients provided responses that fell into four conceptual categories labelled as “suffering from side effects,” “striving to cope with side effects,” “hoping for treatment efficacy or relief from side effects,” and “care appraisal.”

“Suffering from side effects” covers a range of symptoms varying in frequency, intensity or severity, and controllability, which may be physical, psychosocial or role disturbances; “striving to cope with side effects” reflects psychological strategies for managing side effects; “hoping for treatment efficacy or relief from side effect” expresses expectations about treatment benefits; and “appraisal of care” covers trust encouraging toleration of side effects, or disappointment (among patients who had stopped treatment) resulting from the realisation of disease progression and treatment failure.

Figure 1 depicts the relationships between these conceptual categories with respect to patients’ perceived tolerance of side effects in phase I trial of MTAs with/without chemotherapy. Among patients remaining in the trial, treatment was currently perceived as fairly tolerable even if they experienced burdensome or painful side effects. For most respondents, whether still in a trial or not, treatment discontinuation could not be justified by the non-tolerance of treatment side

effects and the actual decision for the discontinuation of treatment was to be made by the healthcare professional.

These categories are further described and illustrated under the following subheadings.

3.1.1 | Suffering from side effects

Patients experienced a range of side effects which were described as having varying degrees of intensity, and as more or less bothersome, unpleasant, annoying, uncomfortable, burdensome, hard to bear or painful. Some patients wondered about the aetiology of their symptoms without always clearly attributing them to the current treatment.

P12—We’re bound to be tired and there are side effects that are linked to the treatment... What are they caused by? We don’t know... I have problems with my white cell count, which are still low, but that’s not because of the new molecule, it’s um..., diarrhoea problems...but there aren’t that many side effects—and there’s pain, a bit sharp but not very frequent... Well.... I don’t have that many side effects. Compared to other [treatments], I don’t have that many more.

P11 (FU)—I was not surprised [by the appearance of side effects]... There was a whole list [provided in the clinical trial information leaflet]... Vomiting, spots or fatigue can occur... I was given an ointment that really helped the treatment of my spots... but the vomiting was hard, really hard... It always happened after I had taken my medication... 2 to 3 minutes after, it would rip my guts apart... I had to walk around with a basin in my hands...

The side effects described as the most “intolerable,” “unacceptable” or “unbearable” were those with the heaviest impact on daily activities.

Among the most significant aspects for patients, *no longer being able* to carry out one’s activities (or not in the way they used to) was described in terms of loss, leading to complicated adjustments on a daily basis, and also to changes in self-image and in social roles and social interactions.

These impacts could affect life in general by confining subjects to an inactive-passive role. A state of this type seemed to be particularly distressful because it affects the person’s self-image and values of autonomy. Whether or not these impacts were currently present, they were described as the consequences of the treatment that were the most difficult or hardest to bear, whereas *being able* or *not being restricted* was another way of saying that “things are fine.”

P02—It put me in a state [passive state] that wasn’t like me before the start: I didn’t feel ill before the treatment, but now I do feel I’m ill.

P02—I no longer recognise myself because I’m very tired, I can’t do activities I used to do, so that’s complicated to handle, psychologically.

TABLE 1 Socio-demographic and clinical characteristics of patients

Patient	Age band at interview	Gender	Tumour type	Years since diagnosis	Months since inclusion	Number previous cycles/days	Treatment	Toxicity >grade 2	Toxicity = 1 reported over >4 cycles
<i>Participants (N = 17)</i>									
P01	60–69	M	Nasopharyngeal	17	3	5	Demethylating agent	Alopecia, asthenia, neuropathy, sinusitis, vomiting	–
P02	40–49	F	Choroid melanoma	4	3	5	PKC inhibitor	Acne	Asthenia, dysgeusia, nausea, cutaneous rash, orange-red urine, vomiting
P03	60–69	M	Choroid melanoma	3	3	5	PKC inhibitor	–	Constipation, orange-red urine
P04	60–69	M	Choroid melanoma	7	2	4	PKC inhibitor	–	–
P05	50–59	F	Choroid melanoma	16	6	8	PKC inhibitor	Constipation	Acne, asthenia, dysgeusia, nausea, orange-red urine, vomiting
P06	60–69	M	Choroid melanoma	14	8	10	PKC inhibitor	Diarrhoea	Acne, anorexia, asthenia, dysgeusia, bowel movement disorders, orange-red urine
P07 ^a	50–59	F	Choroid melanoma	6	4	5	PKC inhibitor	Asthenia nausea	Dysgeusia, nausea
P08	40–49	F	Choroid melanoma	12	7	9	PKC inhibitor	–	Asthenia, diarrhoea, dysgeusia, nausea
P09	50–59	F	Breast cancer	3	1	3	Trastuzumab Entansive ± Capecitabine	–	Asthenia
P10	70–79	F	Breast cancer	9	11	17	Trastuzumab Entansive ± Capecitabine	–	Anorexia, thrombopenia
P11 ^a	60–69	M	Choroid melanoma	7	2	3	PKC inhibitor	–	–
P12	50–59	F	Breast cancer	10	1	3	CSF1R inhibitor	–	–
P13 ^a	40–49	F	Cervical cancer	13	2	5	PD1 inhibitor	Nausea	–
P14 ^a	70–79	F	Breast cancer	22	3	2	Progesterone antagonist	–	Alopecia, asthenia
P15 ^a	60–69	F	Breast cancer	8	3	2	Progesterone antagonist	–	Neuropathy
P16 ^a	60–69	F	Endometrial cancer	2	3	2	Progesterone antagonist	Thromboembolic event, cough, asthenia, anaemia	Pain, cough
P17 ^a	60–69	F	Cervical cancer	2	6	4	Progesterone antagonist	–	Asthenia, cough
<i>Non-participants (N = 6)</i>									
NP1	70–79	F	Ovarian cancer	2	1	6	Bispecific anti-VEGF/ anti-ANG2 antibody	Arterial hypertension	Arterial hypertension, thrombocytopenia
NP2	60–69	F	Choroid melanoma	2	1	3	PKC inhibitor	–	Diarrhoea
NP3 ^a	20–29	M	Leiomyosarcoma	2	2	5	Monoclonal antibody targeting CSF1r	Pain, mucitis, dysphonia	Anaemia, cough, dysphonia

(Continues)

TABLE 1 (Continued)

Patient	Age band at interview	Gender	Tumour type	Years since diagnosis	Months since inclusion	Number previous cycles/days	Treatment	Toxicity > grade 2	Toxicity = 1 reported over >4 cycles
NP4	40–49	F	Breast cancer	5	2	3	Paclitaxel + AKT inhibitor	Alopecia, anaemia, diarrhoea, GGT increase	Diarrhoea, cutaneous rash
NP5	40–49	F	Breast cancer	3	1	3	Paclitaxel + AKT inhibitor	Diarrhoea, cutaneous rash, cytolytic, GGT increase, neutropenia leukopenia	Diarrhoea, cutaneous rash
NP6	40–49	F	Nasopharyngeal carcinoma	3	2	3	Demethylating agent	Thrombocytosis	Nasal secretion, nausea, dysgeusia, diarrhoea

^aTreatment discontinued.

The perception of the impact of treatment on daily activities was predominantly related to the physical effects it induced.

P06—Take nausea, for example... that was something, I couldn't get used to it. For one thing, it was unpleasant, and... and... with time it became painful, because all this area [the patient feels his abdomen]... there's irritation, so it's really unpleasant.

P08—Water, I can't drink water any more. Still water. It's ... horrible. It... leaves a taste in my mouth... that's really... really unpleasant. It was the same for the taste of food to start with, but then it got better.

For a respondent to consider the side effect intolerable, it had to affect the social or psychological domains of life.

P02—I couldn't take it any more psychologically. It was hard physically, but also psychologically, I was at the end of my tether, because, well it's unbearable, that's not how life should be [laughs] being in that state!

P02—When your children see you vomit every day, it is not very easy, and my husband too ... It's complicated for everybody.

P02—Tiredness bothers me because I don't have a social life. Well, not as much as I used to! Work is part of my social life. So I have difficulty projecting myself, and that's not funny, avoiding making too many plans, at least professional plans, because I still try to have personal, family plans, for my children, for myself, but then I don't know what shape I'll be in, in 3 or 4 months' time. It might get better; that would be nice. But tiredness is always there and it doesn't seem to decrease much. So I don't know. It's difficult to make commitments to people who count on you.

Factors that could lead to the perception of the side effects as being difficult to tolerate also concerned their number, frequency, intensity and controllability. Nausea and vomiting was often experienced as the worst side effect on account of its frequency and the resulting pain. Dysgeusia was felt as "unpleasant" and was considered either as "nothing much" or as "bothersome."

P02—When you have nausea every morning, and when it lasts all morning, it's...pfff... no. Well.... If it happened only once in a while... but it doesn't, it's every day. Every day I know that when I take my medication... Mind you, it doesn't always have the same intensity. There are certain moments when it's more bearable and manageable than others.

P08—When there was vomiting for example, when I was frequently vomiting, after a while it gets really wearing... I

find it's the hardest thing in fact. (...) You go out wondering "am I going to be sick?" just now I knew I wasn't feeling that well,... Anyway, it's not serious... but... it does hamper things, it's never very pleasant...

P06—But anyhow, I got used to it [loss of appetite due to dysgeusia], it's not a problem...

Fatigue, diarrhoea, constipation, skin problems (pimples), weight loss, orange urine and pain in limb extremities were the other side effects mentioned. Most of these symptoms caused social isolation and were anxiously anticipated.

P06—Take eating for example [loss of appetite due to dysgeusia], it's a problem for me, because... it prevents me from having a good time, because I used to be someone who had a "heartly appetite" as we say... Now I am not able to share moments of this kind...

P06—Simply the fear of having this nausea on the train coming here. Or in the car (...) It's true, it did worry me a lot.

The experience of "suffering" also seemed to be determined by the absence of any means to treat, reduce, alleviate or avoid the side effects. Not being able to control them could be felt as distressful because of the resulting feeling of helplessness.

P02—Even if I can't control fatigue, I am able to stop myself at some point and take a rest, since it is what my body is asking at that moment. It's a time for a break. But with nausea, it's not the same, it's physical, really, there is a pain or a really, very unpleasant feeling. You feel that your stomach is attacked and suffering. At moments like that, I feel helpless and I have no means to alleviate the feeling—apart from throwing up, which I have experienced as a relief sometimes. Also [with nausea], I have no means of action, whereas with fatigue, well, I stop and I allow myself a break (...) I suffer less, in fact.

3.1.2 | Striving to cope with side effects

Faced with a number of side effects variable in their course, intensity or frequency, patients turned to different psychological strategies that helped them adjust (e.g. finding practical solutions) or accept these side effects, or to obtain alleviation.

Having to "overcome," "deal with" or "live with" side effects in order to better tolerate them was mentioned when participants talked about side effects that were inadequately controlled or burdensome (although medically treated).

Feeling an obligation or a duty to cope with side effects was noted in patient's discourse and seemed to reflect a form of resignation or constraint.

P06—We're always battling with that! Trying to recuperate and finding the impetus to go further ... it's a battle, it's my battle in fact: giving myself the courage to go further. Every day.

P07 (FU)—You look at the tablets and then you say to yourself—well, I must take them... I must for my children, my husband...

Among patients pursuing treatment, a process of putting side effects into perspective by comparing them over time, comparing treatments or physical states between one patient and another, was observed.

P10—When I see some people, they are really not well... really; so ... I am not that bad.

P04—The fact is, I can carry on with my activities ...; these side effects are not much right now. It's nothing at all, I'm telling you: in comparison to the other [treatment], it's nothing at all.

P05—There are some side effects, but... compared to everything I endured from [other] treatments, which were clearly harder, I can put things into perspective. Well, there are days when it's a little harder sometimes or... but I manage to put things into perspective...

This could lead to minimise side effects in reference to past or worse experiences. Current side effects seemed more bearable in contrast.

P05—All in all, I don't have that many ... To be honest, compared to the other treatments that I've had... I can't say it's nothing because there are some, but compared to what I've experienced, I find it much easier to manage.

Being resigned to side effects was also observed as an avoiding coping strategy based on the need to avoid thinking (too much) about side effects. The need to "struggle for a normal life," live as normally as possible, without being overwhelmed by the disease and the side effects, was stressed.

P10—... I have a phrase... which is "struggle for life" ... at times it's a survival instinct; it is how I function; I have always been a fighter... Then I try to enjoy life... I am not the kind of person who cries over myself ... It is both instinctive and intentional.

3.1.3 | Hoping for treatment efficacy and symptom relief

Patients who continued treatment felt that the first weeks in the clinical trial were difficult, but experienced symptom improvement. They sometimes reported that they were *feeling better now* compared

to a few weeks, months, or years ago, and hence that the current treatment was more tolerable or less burdensome than a previous one. They explained this as a spontaneous reduction in side effects, whereby the body was getting used to the drug. Symptom relief could also be derived from medical care.

P01—At the start, it was really heavy going. It was like chemotherapy. (...) It was really, really heavy going, very tiring, very heavy going. At the end of the third cycle (I'm currently on the fifth), my dose was decreased and I now only take two pills. But it was quite difficult.

P01—No, at the beginning, I also had digestion problems. I had a lot of diarrhoea, there has been much less now for 2 or 3 weeks, hardly any diarrhoea at all.

P04—There is always hope that the body will get used to it, because the... the pills I was taking, for other people they didn't have side effects. So, you think: "well, maybe there is a period of adaptation for the body and these side effects will disappear little by little." And ultimately, no, for me they didn't disappear.

Patients also expected benefits from treatment although it seemed that they were not taken by the illusion of a possible cure but rather were expecting improvement of symptoms and functioning.

P10—[What do I expect from this treatment?]. Well, to get cured. But I'm coming to terms with the fact that it's a very long process and that it may not be curable. At the moment, I know it's stabilised but I'd like to be cured 200%. I want to get back to my former weight, my muscles and to do what I want. Because at the moment, I'm still rather limited...

Some patients did not experience any side effects. This led them to doubt the efficacy of the treatment and they wondered how long they had to live. Compared with the cytotoxic drugs they had previously, MTAs could be perceived as less effective since treatment side effects had been announced and were actually experienced as less severe.

P05—I don't have any side effects that are too serious. Either my body is getting used to them or... perhaps it's because...I'm trying to cope with them better, but I don't have any side effects that are too serious.

P13 (FU)—I was delighted to be eligible for this treatment ... because the chemo was no longer effective... but these targeted therapies are less effective ... they have fewer side effects.

P14 (FU)—Before the doctor told me that we should stop the treatment, I knew that it had no effect... I did not have

any side effects; I could feel that the treatment was not working.

Patients expressed a firm determination to receive the treatment on trial despite the side effects induced, especially because they perceived it as the last anti-tumour option for their cancer. They said how delighted they had felt when they were told that they were eligible for the clinical trial and how disappointed and regretful they were if told that they had to discontinue the treatment protocol, usually due to progression of the disease indicating treatment failure.

P16 (FU)—I was confident, I believed in that treatment... Then I have been more than disappointed... the [treatment] effects were progressively worse, my health deteriorated, I got worse and worse...

3.1.4 | Care appraisal

The importance of good quality of care was underlined. Patients' trust in the medical staff was perceived as a prerequisite to hope and confidence at a time of living in uncertainty of a clinical benefit.

P03—I tolerate the treatment very well ... I trust the doctors; I trust when people are good at their jobs.

Patients who pursued treatment felt that since the treatment was tolerable at the moment, they would just put their trust in the medical staff. Being able to rely on caregivers seemed to help patients not to worry about side effects, and simply comply with treatment and hope.

P01—From then on, you chose to trust them, you get treated, you follow on with it.

Among patients who had to discontinue treatment, clinical evidence of illness progression and the resulting need to stop treatment led to disappointment, which was associated with negative appraisals of care. Feelings of regret at having agreed to participate in the clinical trial, lack of information enabling an anticipation of symptoms, illness progression or treatment response were expressed.

P14 (FU)—I regret that we did not stop the treatment earlier because it was not effective, I did not feel any side effects; the treatment was too weak... I lost 3 or 4 months of my life...

3.2 | Treatment discontinuation

When asked about what made their treatment intolerable or what would make them want to stop it, patients continuing the clinical trial mentioned their experience of a good tolerance in the here-and-now. In some cases, they also underlined that they did not have that experience or did adapt to the side effects.

P01—If I had not been able to stand it, I would certainly have had side effects telling me “stop everything”! [Q: What sort of side effects would tell you that?] I don't know. I haven't experienced it so I can't tell you!

Side effect tolerance could vary over time and the frequency of side effects was sometimes related to treatment acceptability and thoughts of dose reduction or discontinuation of the treatment, but retrospectively, only a minority of patients reported having thought of stopping the treatment.

P02—The doctor told me that I should normally have vomiting episodes only about once a month. At the moment I still have one to two vomiting episodes per week... And he told me that it was still not acceptable. [Q: Did you think about stopping or asking for a decrease in the dose?] Yes I did. I thought about stopping when I was vomiting every day. That was unacceptable; in the end it had become intolerable. I was really, really unwell. In fact it transpired that I was suffering from serious anaemia... After the transfusion, treatment was resumed.

For one patient, stopping the treatment seemed conceivable under certain conditions, especially if he/she could go back on his decision.

P04—Yes, I would have contacted the [Clinical Unit]... yes, so long as I could... [envisage another treatment]. You just need to ask to stop... and try something else. You have to...

For some patients to consider treatment discontinuation clinical evidence of illness progression or the lack of treatment response was required, rather than patients' subjective perception of the unbearable nature of the side effects.

P7 (FU)—Tiredness is more tolerable when you think it is because of the treatment rather than the illness that is progressing... I don't know if there are cases where the patient can't take it any longer and would stop the treatment as a result... You don't stop because the side effects have become intolerable; it's because the illness is progressing that side effects become intolerable.

P7 (FU)—I didn't ask to stop, but the illness got the upper hand.

P16 (FU)—Treatment discontinuation was decided by the Clinical Research Unit... I had thought about stopping but I had made a commitment... I believed in that treatment... at least that one... I thought that the side effects would get better... I asked myself whether it was tolerable or not, whether the treatment was effective or not ... what to expect? Was the treatment not working or was the disease

spreading? I was relieved when treatment discontinuation was decided on but I was disappointed... I needed a break...

They expressed their wish to pursue treatment as far as possible, dreading they might regret a personal decision to stop treatment. Discontinuation of the treatment was sometimes perceived as a renouncement, at odds with the determination to go on to the end, and it, therefore, seemed impossible or difficult to accept.

P07 (FU)—I wanted to go on to the end so that I wouldn't have any regrets, I wouldn't blame myself, I wouldn't tell myself “I didn't have enough courage”... in that way I wouldn't feel guilty...

This difficulty sometimes stemmed from the feeling of having few treatments available and the fear of running out of options and therefore of no longer being able to obtain a lengthening of life expectancy (hence the absolute necessity to “find something else”).

P12—But in fact, you tend to favour the all-out solution. I don't know what other people are like, but I rather think to end to be all-out. That is to say... not until things actually break up, but ... holding out as long as possible. Because you don't have that many treatments ahead of you. And you know it! There it is.... And every treatment ... is like a presence here. On Earth. There we are.

P08—If this one doesn't work, well yes, in any case, we'll have to find something else. There's no choice. But, as I understand it, there aren't that many treatments for this case... my case... my particular case in this type of cancer, so... I don't know. I'll just wait and see.

Few patients said that the treatment was so intolerable that they would actually ask for a dose reduction or discontinuation. There seems to be a big difference between “thinking about stopping” and “asking to stop.” This distance was manifested in the distinction between “saying stop to oneself” and “saying stop.” While it was considered important to feel ready to “say stop to oneself” and to set personal limits, it appeared difficult to imagine what could lead to “saying stop.”

P12—You've got to ask yourself: a treatment that works, with lots of side effects ... and that you discontinue... we are happy when it stops, and at the same time, we think, um... when it becomes unbearable, we have to stop... it's not clear in my mind (...) And I think there must be a time when we say to ourselves: “right, stop”; but... “stop,” what makes you say just “stop”? ...

It seemed important to them to be able to rely on the clinician for the decision to discontinue treatment.

P08—I think that if there was really too much vomiting and they weren't able to control it, I think that in any case the doctors themselves.... after a while...

P11 (FU)—The doctor decided to stop the treatment because the vomiting was more and more severe and uncontrollable... I lost 8 kg in a few weeks... since I was so ill, we had to deal with it [the symptom].

P12—The medical staff don't leave us with side effects that are too serious. They discontinue. Even if it's working.

4 | DISCUSSION

A range of symptoms of varying frequency or intensity were mentioned by patients in relation to their experience of *suffering from side effects* which was essentially due to the functional and psychosocial impacts of physical symptoms. This suggests that *global* HRQL questionnaires may be needed to assess the degree of bother associated with treatment toxicities (Cox, 2003; Eton et al., 2006).

Patients who pursued treatment reported fairly acceptable treatment tolerance even if they experienced burdensome or painful side effects. In fact, these patients presented good vital functions, which are also an eligibility criterion for entering phase I clinical trials (Rouanne et al., 2013). Their side effects may also have been efficiently controlled. Likewise, adaptive psychological reactions, perceived good care quality and trust also appeared to help them deal with treatment side effects. It has been suggested that psychological adjustment to health change results in a "response shift phenomenon" when one's health status is assessed (Korfage, Hak, de Koning, & Essink-Bot, 2006; Rapkin & Schwartz, 2004). The perceived good treatment tolerance by patients in this study may relate to this phenomenon.

Patients pursuing or having discontinued treatment reported comparable experiences and reactions to symptoms and clinical trial protocols. However, disappointment and dissatisfaction with care was sometimes expressed by patients whose participation in the phase I clinical trial had been discontinued.

For patients whose treatment was discontinued, even when side effects were described as very difficult to bear, stopping treatment or asking for a dose reduction was hard to contemplate. Having placed major hope in the treatment, they felt deeply disappointed when faced with the clinical evidence that the treatment was not effective. This is in line with previous research findings showing that more than 90% of patients said they would still participate in the study even if the phase I experimental drug caused serious adverse effects (Agrawal et al., 2006). This may be related to an unrealistic optimism (Agrawal et al., 2006; Miller & Joffe, 2013) or to the "therapeutic misconception" phenomenon (Godskesen, Nygren, Nordin, Hansson, & Kihlbom, 2013; Miller & Joffe, 2013) by which patients may confuse research with treatment and believe that they will receive therapeutic benefit from study participation (Matutina, 2010).

Phase I trial cancer patients may face up to painful side effects because of their determination to pursue the experimental treatment. Consequently, they often take the medicine even though they suffer from side effects.

From a clinical point of view, given this observation and also research results showing that clinicians often underestimate the frequency and severity of certain side effects as compared with patients' self-reports (Di Maio et al., 2015; Novello et al., 2014), it is possible that some patients are treated with doses that are too high, rather than optimal for them.

From a scientific viewpoint, it is expected that the assessment of patient-perceived treatment tolerance will help in defining dose-limiting toxicities in phase I clinical trial on MTAs. However, from this assessment of side effect tolerance seen from the patient's point of view, it seems that patients' hopes invested in a "last-chance" treatment and their coping strategies might lead to a risk of bias and incorrect results. Underreporting side effects may result in unnecessary adverse effects, excessively prescribed doses in routine practice or choice of a treatment dose that is too high rather than optimal when weighing treatment response against toxicity and this may also affect phase II trial participants. At a later stage, in clinical practice, these side effects could result in poor treatment adherence over time which could compromise efficacy (Blay & Rutkowski, 2014; Efficace et al., 2012).

Theoretical definitions of "tolerability" have been provided. From the medical point of view, the term "tolerability" refers to the fact that "... [the drug] accomplishes all of its purpose while retaining an excellent safety profile, with low incidence of side effects" (Fortier, 1994). From the individual's viewpoint, "tolerability" has been defined as "the point at which an individual is not willing to accept a stimulation of a higher magnitude" (DiMatteo, 1991). Our study results question the validity of these definitions: although patients can experience painful side effects (incidence), as long as these treatments do not entail adverse clinical events (safety), they may be continued (acceptance of drug dose).

Ethical considerations can also be raised. Patients with advanced cancer having exhausted standard treatment alternatives and enrolled in a phase I trial appeared to choose to be treated in an "aggressive" manner—as a last chance and with the hope of therapeutic benefit. Even though phase I clinical trials may result in objective tumour response as evidenced by CT scan image data (Horstmann et al., 2005), the primary aims of these trials are to evaluate toxicity and dosage for subsequent efficacy studies and only a minority of phase I patients will evidence tumour response. For patients, the drug tolerance threshold may be high although a clinically efficient drug in subsequent trial phases might be obtained at a lower dose than the patient's defined tolerance threshold.

Patients harboured inappropriate beliefs associated with the trial (e.g. experiencing side effects means the treatment is effective; the higher the drug dose provided the higher the chance of obtaining physical benefits) and expectations (e.g. the body will get used to side effects), which suggests the need to enhance the provision of information and to ascertain its comprehension by study participants (Jenkins

et al., 2011; Miller & Joffe, 2013). A clinical trial question prompt list could be useful to encourage patient questions (Brown, Butow, Boyle, & Tattersall, 2007) and to address misconceptions about treatment or prognosis (Jenkins et al., 2011). Frequently asked questions may also usefully complement the information document related to the clinical trial.

Finally, patients could show and report fairly good treatment tolerance despite burdensome or painful side effects. This may cloud healthcare professional judgement (and possibly lead to underestimate patients' side effects). Moreover, they seemed to refer to doctors for the decision of treatment discontinuation. Training in consultation skills may help facilitate exploration of patients' experience as well as install a collaborative communication (Butow et al., 2015) to discuss the hierarchy of competing objectives, such as life prolongation versus comfort, in a supportive environment.

4.1 | Limitations

This study is limited by the fact that patients in our sample mostly shared the same clinical MTA trial protocol (PKC inhibitor for those who pursued treatment or progesterone antagonist for those who had to stop) and so our results may not extend to any phase I trial of MTAs. Moreover, this study does not make it possible to determine which type of treatment (one of the MTAs or chemotherapy) caused the side effects mentioned by patients; however, it may be generally difficult to distinguish the symptom aetiology in patients affected with advanced cancer who have already benefited from different treatment regimens.

We did not look for cases that would contradict our theoretical proposals. However, following data saturation on a systematic analysis, we have provided an in-depth understanding of the experience of treatment tolerance in the context of phase I clinical trials. To enhance the validity of the results, data interpretation was checked, in a triangulation process, by involving the perspectives of the multidisciplinary research team members (Mays & Pope, 2000).

4.2 | Conclusions

Treatment tolerance in the discourse of patients included in a phase I clinical trial of MTAs appeared to be linked not only to the functional, psychosocial and physical impact of side effects but also to psychological factors such as coping strategies, motivations for living, and perceptions of the care and treatment provided. For patients, stopping treatment had to be motivated by the absence of treatment response rather than any subjective intolerance of side effects. The adequacy of patient reports on their perceived tolerance in determining an optimal drug dose for phase II trials can be questioned, given that in the context of phase I trials, patients can endure severe symptoms in order to benefit from a last-chance treatment option. Hopes and misconceptions among patient in phase I trials health are a challenge for care professional-patient communication and require facilitating psychosocial interventions.

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CONFLICT OF INTEREST

The authors indicate no conflicts of interest.

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