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Review

Understanding cognitive processes behind acceptance or refusal of phase I trials

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ABSTRACT

Participation in phase I trials gives patients the chance to obtain control over their disease by trying an experimental therapy. The patients' vulnerability, the informed consent process aiming at understanding the purpose and potential benefits of the phase I trial, and the complexity of the studies may impact the patient's final decision. Emotionally difficult health conditions may induce patients to succumb to cognitive biases, allocating attention only on a part of the provided information. Filling the gap in patients' information process can foster the implementation of strategies to help physicians tailor clinical trials' communication providing personalized support and tailored medical information around patients' need, so avoiding cognitive biases in patients and improving informed shared decision quality.

The aim of the present review article focuses on the analysis of cognitive and psychological factors that affect patients' decision to participate or not to early phase clinical trials.

1. Introduction

Milan, Tuesday 9.40 am. Patient: "Doctor, I am very worried about the CT scan report. It says 'disease progression'. 'Progression' means that the treatment I'm receiving is useless, isn't it? Does that mean I have no opportunities of treatment anymore?" Doctor: "The conventional treatments do not show any benefit, this is true. However, we can offer an experimental therapy. We have several phase I trials ongoing".

Besides the standard therapies, there is considerable leeway for clinical trials in the setting of uncertainty. Clinical trials may currently enable patients to benefit from treatment de-escalation or from specific personalized targeted therapies in the advanced setting. However, the rate of patients included in clinical trials in

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Western countries has been reported to be less than 10%. This rate varies according to the type of clinical trial and the disease stage (Go et al., 2006; Lara et al., 2001). The arguments for non-inclusion concerned both physicians and patients and were multifactorial, including social, racial, educational and demographic reasons (Mills et al., 2006). Moreover, independent of country and/or social-cultural characteristics of patients, cancer treatment experience is emotionally distressing. Three major themes should be identified to explain distress: (a) the "losses" associated with diagnosis of cancer, (b) the impact beyond the patient and into the patient's family, and (c) "coping" with cancer through spirituality and emotional involvement. We frequently apply stereotypical descriptions of cancer perception and acceptance, which illustrate the tendency to generalize cultural behaviors, values, and beliefs in a way that ignores individuality and diversity of any single patient. In order to adopt a real personalized approach, we should open up space to explore patients' experiences, and to bring their voices into the therapy decision-making process (Gorini and Pravettoni, 2011; Pravettoni and Gorini, 2011). Phase I studies are designed to test the safety profile of novel agents and typically enrol patients for whom other treatments have failed. Ethical concerns have been raised about phase I trials, including questions about patients' vulnerability, the burden of study participation, and whether patients and families understand the purpose and negligible likelihood of benefit (Miller et al., 2014; Pentz et al., 2012).

The aforementioned reports mostly concerned medical research in general, or oncology in particular. But there is a lack of studies specifically devoted to the early phase I setting in oncology, despite the fact that patients' participation rate in phase I trials is even smaller (Brown et al., 2013). This is certainly due by the nature of phase I trials themselves because, in most of cases, their primary aim is not to cure, but to test starting dose and toxicity of new drugs. Considering that patients who are proposed to participate are going to face uncertain (if any) benefits, and potential side effects, many ethical concerns have been raised regarding their participation. The main reason for such concerns is related to an assumed lack of patients' understanding of provided information and therefore of risks and benefits. However, in the area of new "targeted" agents, the biologically effective dose is frequently used instead of the Maximum Toxicity Dose (Mahipal and Nguyen, 2014). Phase 1 clinical trials aimed at testing targeted therapies have shown positive responses in many diseases where traditional therapies failed. The era of phase I clinical trials is moving from cytotoxic therapies toward precise, rational and targeted therapies leading to an increase in likelihood of treatment response. In this perspective, in the economics of the disease, phase I clinical trials are anticipated in order to have a patient's profile in which toxicity due to previous treatments is reduced and to increase the probability to obtain a benefit from the treatment.

In line with this new perspective, a change in the conceptualization of phase I clinical trials requires a change in the way they are proposed. A first step in this direction is to understand how patients process information and what factors affect their decisions to accept or refuse to participate.

This review outlines the evidence for the underline cognitive and psychological factors. Existing and challenging strategies to enhance informed decision quality are also discussed.

2. Method

We carried out searches in MEDLINE, EMBASE, and Cochrane Library for papers published until April 2015. The following keywords or combinations were used: 'phase I clinical (or oncology or cancer) trial' and psycholog*; cognit*; bias*; emotion; 'information process'; understand* and decision*.

This review presents two main sections: the first one describes the psycho-cognitive variables involved in the decision to participate in phase I oncology trials; the second section relates possible methods and tools to improve patients' knowledge and participation.

3. Participation to phase I oncology trials

Some studies investigating the reasons for participating in phase I clinical trials showed that volunteers are desperately looking for an effective intervention and might not realize the very low chance of personal clinical benefit (Cox et al., 2006; Estey et al., 1986; Jenkins et al., 2010; Smith et al., 1996; Von Hoff and Turner, 1991), rather they tend to be unrealistically optimistic hoping or expecting a direct positive benefit from the treatment (Miller et al., 2013). This optimistic bias, however, is not associated with a misunderstanding of the purpose of the trial (Jansen et al., 2011). However, Agrawal et al. (2006) demonstrated that patients are aware of both the aim and the limits of oncology trials, and "want to fight aggressively until the end". Coherently with these findings, many patients volunteer in phase I clinical trials aware of the modest benefits and expressing expectations for the outcomes that exceed those of physicians (Collins et al., 2009). On the other hand, a reason for denial is patients' perception to be less informed and less supported in the decision-making process with a consequent higher decision conflict compared to patients who accept to participate (Flynn et al., 2008). Among other factors, trust in the clinical study team seems to be the precondition for participation in research (Djulbegovic and Hozo, 2012; Miller and Weijer, 2006; van der Biessen et al., 2013). In this perspective it is not important what it is said but rather how it is said and what are the physician's beliefs about the treatment and his or her hopes for the patient (Miller et al., 2014). Finally, many others patients decide to participate for an altruistic reason and the possibility to help future patients.

4. Concerns related to acceptance or refusal of phase I oncology trials

Several questions arise around motivations of patients participation in phase I oncology trials. Since the participation rate of adult patients with cancer is small, there might be a preconception that ethical principles apply only to decision to participate, while patients who spontaneously refuse to be included in the trials do not receive further consideration.

We propose to focus more attention on this population, in order to have a complete picture of the factors affecting the specific decision-making process. This approach will favor the implementation of strategies to improve decision quality, according to Collins' three principles that a choice should be: (a) informed, (b) coherent with patient's values, (c) acted on, the first being the factor affecting and improving the other two (Collins et al., 2009).

In a recent study (Pentz et al., 2012), authors explored trial refusal reasons in a group of African American patients with cancer who declined trial participation and gather patients' perceptions of the potential benefit of an array of decision support tools. Most patients refused as a result of fears of additional burdens and adverse effects. Many patients and also family members misunderstood trial information. As consequence, family members recommended patients against trial participation. Most patients felt that question prompt lists or decision aids would assist information seeking and decision making. Lack of trust in medical research has been identified as a primary reason for patients refusal to participate in clinical trials.

The issues emerged in the aforementioned studies underline the need to deeply understand patients' decision making process.