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Evaluation of the quality of the reporting of phase II clinical trials in oncology: A systematic review

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ABSTRACT

Objective: To describe the current state of knowledge concerning the quality of reporting in phase II clinical trials in oncology and to describe the various methods published allowing this quality evaluation.
Methods: databases including MEDLINE and COCHRANE were searched. Reviews and meta-analyses analyzing the quality of the reporting of phase II trials in oncology were included. Descriptive analysis of the results was performed.
Results: Thirteen publications were retained. Only 2 publications adopted a systematic approach of evaluation of the quality of reporting by overall scores. The Key Methodological Score (KMS), proposed by Grellety et al., gathering 3 items, seemed adapted for such an evaluation. A score of 3/3 was found in 16.1% of the 156 phase II trials analysed by this score. The other reviews used a qualitative analysis to evaluate the reporting, via an analysis of a single criterion, generally the statistical plan of the study. This item was considered as having been correctly reported in less than 50% of the analysed articles.
Conclusion: The quality of reporting in phase II trials in oncology is a field that has been investigated very little (13 publications). When it is studied, the estimated level of quality is not satisfactory, whatever the method employed. The use of an overall score of evaluation is a path which should be pursued, in order to get reliable results. It also seems necessary to propose strong recommendations, which would create a consensus for the methodology and the reporting of these studies.

1. Introduction

In oncology, phase II clinical trials play a key function in the development of new treatments and/or new therapeutic strategies. They aim at investigating the effectiveness and the toxicity of an experimental treatment or a combination of treatments. The objective is to select the molecules justifying the realization of a phase III clinical trial, thus ensuring the role of a "filter". These tests are carried out on a very selected population of cancer patients.

Currently, in the field of oncology, the treatments that are candidates for phase III trials and those which are candidates for the obtention of an authorization to be marketed, are multiplying, particularly since the advent of targeted therapies. Parallel to this, oncology proves to be the specialty which has the highest attrition: the highest number of molecules whose development is interrupted, taking all the stages of the drug development into consideration (Kola and Landis, 2004). At the stage of phase III trials in particular, oncology shows an average rate of attrition superior by 11.3%–4% in comparison to the average rate of attrition known in other specialties (Kola and Landis, 2004; DiMasi and Grabowski, 2007). These observations imply that the selection of experimental treatments under development in phase II trials, is of lower quality in the field of oncology, compared to that in other specialties. Phase III trials are more expensive and may cause a potential loss of chance for the participating patients when they prove to be negative. This observation, concerning the rate of attrition of the molecules in oncology, which is higher in phase III, must lead to the creation of procedures for the evaluation of the quality of the previous stages of the therapeutic development: phase II trials.

Contrary to the controlled randomized clinical trials, whose drafting is supervised by the CONSORT recommendations which are regularly

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updated (Begg et al., 1996; Moher et al., 2001; Schulz et al., 2010), in the case of clinical phase II trials in oncology, there is no consensus of precise and specific recommendations for the reporting and drafting of these trials. This is also the case when it comes to having a validated score of evaluation for methodological quality. However, Ivanova et al. (2016), showed that the phase II trials in oncology, which described the statistical design of the study in an incomplete way, presented a significantly higher probability of concluding positively on the effectiveness of the studied molecule. Whereas many other issues (as the large number of drugs tested, the historic low therapeutic index of cytotoxic agents, the costs related to treatment development or the lack of biomarker strategy to support patient stratification) may explain the high attrition rate in oncology trials, this tends to suggest that the quality of the reporting in the publications of phase II trials in oncology could have an impact on the future of the development of the experimental treatment.

The assumption that the strong rate of attrition in the clinical phase III trials in oncology can be, at least partly, explained by the methodology of the phase II trials, led us to carry out a systematic literature review, with the objectives of making an inventory of the publications having analysed the quality of the reporting of the clinical phase II trials in oncology, and of describing the various methods available for a reproducible systematic evaluation of the quality of the reporting in these studies.

2. Methods

2.1. Selection of the articles

The criteria of inclusion of the studies in this review of literature were: publications in the form of systematic reviews of phase II trials in oncology or leading articles or letters to the editor, whose objective were to evaluate the quality of the reporting of methodological criteria. Publications written in both French and English, were retained. There was no limited date for publication selected, with a last electronic request carried out in December 2015. Original articles, as well as the publications which related to a field other than oncology and recommendations, were excluded from the selection.

Research was carried out using the MEDLINE and COCHRANE databases, in order to identify the publications whose subject was related to the analysis of the reporting of the phase II trials in oncology, as well as the different items that are essential for reporting of good quality. The keywords used were “reporting” and “phase II”; the terms “neoplasms” and “Clinical Trials; Phase II as Topic/standards” were used as MeSH terms. The request formulated in MEDLINE was built in the following way: (“Clinical Trials; Phase II as Topic/standards” [MeSH Terms] AND “neoplasms” [MeSH Terms]) OR (“reporting” AND “phase II” AND “neoplasms” [MeSH Terms]). The request formulated in the COCHRANE database was: (“Phase II trial” AND “reporting” AND “neoplasm”); with a filter allowing us to retain only the studies of methodology (“methods studies”).

The selection of the studies was carried out initially on the basis of the titles of articles, highlighted by the request carried out in the MEDLINE and COCHRANE databases. Secondly, a reading of the summaries of the studies selected on their title, followed by a complete reading of the publication if the summary were in adequacy with the objective of our study, were carried out, leading to a final selection. Finally, a manual research in the grey literature was also carried out, using the bibliographical data resulting from the publications retained by electronic request.

2.2. Analysis of the articles

We were able to consult all of the publications retained for analysis, in their full version. A grid for the extraction of the data was built by a multidisciplinary team, composed of a methodologist, a statistician and clinicians. This grid of extraction was then tested and modified, after having analysed 3 of the selected publications (Table S1). The variables were extracted by one of the authors. The data collected for the analyses of the literature which concerned the evaluation of the quality of the reporting were: the year of publication of the study, the name of the journal, the type of publication, the cancer site concerned, the number of analysed articles, the period of selection of the articles, the different items studied, scores or frequency of reporting of the studied items, the factors associated with the variation in quality of the reporting of the studied item and the potential recommendations and/or methodological discussions associated with the review of the literature.

No statistical analysis was carried out in this review of literature. The delivered results were purely descriptive and were expressed as a percentage.

3. Results

3.1. Selection of the articles

The request carried out in the MEDLINE database made it possible to obtain a result of 220 publications. Only 9 of these articles corresponded to our selection criteria and were conserved for analysis. The request carried out in the COCHRANE database did not highlight any article answering our selection criteria. In parallel, manual research in the grey literature made it possible to select 4 publications of interest. In total, 13 articles were finally selected (Lee, 2005; Nickolich et al., 2014; Kramar et al., 1996; Medioni et al., 2000; Perrone et al., 2003; Thezenas et al., 2004; Mariani and Marubini, 2000; Ottaiano et al., 2005; Walter and Krzyzanowska, 2012; Vickers et al., 2007; Riechelmann et al., 2008; El-Maraghi and Eisenhauer, 2008; Grellety et al., 2014). The selection process of the publications of interest is detailed in the flow-chart (Fig. 1).

3.2. Characteristics of the systematic review of literature

Four out of thirteen of the selected publications were published in only one Medical Journal: Journal of Clinical Oncology. These publications were most of the time published over 10 years between 2000 and 2009 (9 out of 13 publications). The oldest has been published in 1996 (Kramar et al., 1996) and the latest have been published in 2014 (Nickolich et al., 2014; Grellety et al., 2014). Most of those reviews (10 out of 13) assessed studies no matter of the cancer site. All of them were reviews but one (Riechelmann et al., 2008) which was a letter. The characteristics of the selected articles is summarized in Table S2 (online only Supplementary material).

3.3. Analysis

3.3.1. Evaluation of the reporting by a score

We focused on studies using a score to assess the quality of reporting, because scores are supposed to be more reliable, valid, discriminant than qualitative assessment. What’s more they are standardized: they eliminate the variation of measurement, allowing generalization and comparison of results (Kline, 1986). Two of the 13 publications selected (15.4%), studied the quality of reporting of one or more criteria with an overall score: Grellety et al. (2014) and Ottaiano et al. (2005). Grellety et al. (2014) developed 2 scores of evaluation. The first score, named Overall Quality Score (OQS), gathers 44 items, each one counting for a point and covering the various sections of a scientific article (Title, Introduction, Methods, Results, Discussion). The section “Methods” was the most detailed, with items that showed particular interest in the aims of the study, in the selection of the patients, the description of the studied treatment, the methods of measurement of the criteria of judgement and with statistical methodology.

In the systematic review carried out by the authors, taking into account 156 tests of phase II trials of oncology published in 2011, the