European Journal of Cancer 52 (2016) 26–32

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Aggregated adverse-events outcomes in oncology phase III reports: A systematic review

Denis Maillet [a], Hui K. Gan [b,c], Jean-Yves Blay [d,e], Benoit You [a,f,g], Julien Péron [a,h,i,*]

[a] *Medical Oncology Department, Centre Hospitalier Lyon-Sud, Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), CITOHL, F-69310, Pierre-Bénite, France*
[b] *Medical Oncology Unit, Olivia Newton-John Cancer and Wellness Centre, Austin Hospital, Melbourne, Victoria, Australia*
[c] *School of Cancer Medicine, La Trobe University, Melbourne, Australia*
[d] *Medical Oncology Department, Centre Léon Bérard, Lyon, France*
[e] *EORTC, 83 Avenue Mounier, Bruxelles, Belgium*
[f] *EMR UCBL/HCL 3738, Faculté de Médecine Lyon-Sud, F-69600, Oullins, France*
[g] *Université de Lyon, F-69622, Lyon, France*
[h] *Hospices Civils de Lyon, Biostatistics Unit, F-69003, Lyon, France*
[i] *CNRS UMR 5558, Biometry and Evolutionary Biology Laboratory, Health and Biostatistics Team, Villeurbanne, France*

Received 9 June 2015; received in revised form 26 August 2015; accepted 26 August 2015
Available online 27 November 2015

KEYWORDS
Methods;
Randomised controlled trials as topic;
Research designs;
Research standards;
Neoplasms;
Publishing standards;
Aggregated adverse events outcomes;
EORTC

Abstract ***Background:*** Randomised controlled trials (RCTs) represent a major source of information on treatment-related adverse events (AEs). In this study, we reviewed the use and the reporting methods of aggregated-AEs (A-AEs) outcomes in RCTs reports published in oncology and compared that to the expectations of European Organisation for Research and Treatment of Cancer (EORTC) membership.
Methods: RCTs reports published between 2007 and 2011 were reviewed regarding the reporting of A-AEs-outcomes. A-AEs were defined as summary outcome combining several related AEs, usually grouped by organ system e.g. cardiac-AEs, dermatologic-AEs. Trial characteristics associated with the use of A-AEs outcomes were investigated. The expectation of EORTC members concerning A-AEs utilisation was queried through a survey.
Results: Among 325 RCTs published between 2007 and 2011, 94 (29%) included one or more A-AE outcomes. A clear description of the nature of AEs included in such aggregations was provided in 19 articles (20%). No description of A-AEs was conversely provided in the other 75 articles (80%). The most commonly used A-AEs-outcomes were dermatologic-AEs (45%) and cardiac-AEs (33%). In multivariate analysis, the use of A-AEs outcomes was more

* *Corresponding author*: Medical Oncology Department, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, F-69310, 165, chemin du grand revoyet, 69495 Pierre-Bénite, France. Tel.: +33 (0)4 78 86 43 18; fax: +33 (0)4 78 86 43 56.
E-mail address: julien.peron@chu-lyon.fr (J. Péron).

http://dx.doi.org/10.1016/j.ejca.2015.08.025

frequent when trials were conducted in Europe ($p = 0.038$) and in trials performed on colon/rectal cancers ($p = 0.016$). Finally, there is no consensus of EORTC members regarding the utilisation of A-AEs but a majority of them (88%) felt that a clear description of A-AEs should systematically be reported.

Conclusions: The use of A-AEs is infrequent in oncology RCT manuscripts although their use is accepted by most clinicians. However, a clear definition of A-AEs is strongly recommended if they are to be used in order to avoid a loss of important details about drug toxicities that is useful to clinicians.

1. Introduction

To optimise the reporting of randomised controlled trials (RCTs) data, the Consolidated Standards of Reporting Trials (CONSORT) guidelines provide a checklist of essential items that should be routinely reported [1,2]. In 2004, the CONSORT guidelines were extended to include 10 recommendations for toxicity reporting [3]. However, adverse events (AEs) reporting remains suboptimal in both oncology and non-oncology trials [4–12]. In medical oncology, new treatment approaches such as molecular targeted therapy or immune-therapy have become dominant during the last 10 years. Many of these newer drugs also have AEs which are completely novel, and sometimes potentially fatal. One of the main source of information about such treatment-related AEs is from the publications of the corresponding clinical trials and hence it is imperative that these should contain clear description of the toxicities encountered [13].

We previously stressed out that quantitative aspect of AEs reporting remains suboptimal [12]. But qualitative problems on AEs reporting also exist and further limit the usefulness of AE reporting. For example, it is sometimes necessary to aggregate disparate AEs into more manageable categories, often based on organ system. This represents one example of how a change in the quality of toxicity report can result in a form of under-reporting. Hence, in this study, we systematically reviewed the utilisation of aggregated-AEs (A-AEs) in oncology RCTs reports published between 2007 and 2011. RCTs characteristics associated with the use of A-AEs were also investigated. Lastly, the findings were compared with the attitudes and expectations of the members of the European Organisation for Research and Treatment of Cancer (EORCT – eortc.eu) about A-AEs reporting in phase III reports.

2. Methods

2.1. Study selection

We identified using MEDLINE via PubMed (http://www.pubmed.gov) all English publications of RCTs assessing systemic anti-cancer therapies published between January 2007 and December 2011 in 10 major oncology journals: *Annals of Oncology*; *British Journal of Cancer*; *Breast Cancer Research and Treatment*; *Cancer*; *European Journal of Cancer*; *Journal of Clinical Oncology*; *Journal of the National Cancer Institute*; *Lancet*; *Lancet Oncology*; and *New England Journal of Medicine*. Exclusion criteria were: paediatric studies; treatment with radiotherapy or surgery only; phase I, II, or IV trials; supportive care, palliative care or prevention trials; meta-analyses, overviews, or publications using pooled data from two or more trials; and secondary reports of previously published trials.

2.2. Data extraction and quality assessment

All abstracts were reviewed by one investigator (JP) for eligibility. Data from all eligible RCTs reports were then independently extracted by two investigators (DM and JP). Discrepancies were resolved by consensus. For the purposes of data extraction, A-AEs were defined by a combination of several AEs (as defined in classifications such as National Cancer Institute of Canada (NCIC) common toxicity criteria) into one composite outcome. The number and nature of A-AEs were assessed for each manuscript. The types of AEs included in such aggregations were also collected if described anywhere in the manuscript. For each article, we also assessed if A-AE outcomes were considered to be clearly described. A-AE outcomes were considered to be clearly described when a clear description of nature/symptomatology of all the AEs components in all aggregation were provided. Moreover, an A-AEs outcome was also considered to be clearly described when a validated definition was used.

2.3. Analysis of covariates associated with the use of A-AEs outcomes

We explored whether the use of A-AE outcomes was influenced by: funding characteristics (solely or partially sponsored by industry); geographic regions; type of investigational therapy; year of publication; journal impact factor; the result of primary outcomes (positive or negative study); the treatment line (adjuvant or metastatic); and tumour type. Univariate and multivariate logistic regression models were built to identify