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Review

Thirty years of phase I radiochemotherapy trials: Latest development

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Abstract Radiochemotherapy is undergoing a complete expansion. Currently, possibilities of treatment combination are skyrocketting, with different anticancer and targeted molecules, different radiotherapy techniques, and dose escalation with each therapy. The development of a modern phase I radiochemotherapy trial becomes more and more complex and should be fully investigated. In the literature, there are no exhaustive reviews describing the necessity of their characteristics. The present article explores historical and current phase I clinical trials involving a combination of radiation therapy and anticancer therapies.

Selected trials were identified by searching in PubMed databases. A total of 228 studies were identified in the last three decades, and a portrait of their characteristics is presented.

As expected, most frequently studied malignancies were head and neck cancers, followed by non-small cell lung cancer and brain cancer. Toxicity is reported in more than 90% of the studies. Most studies were published since 2010, at the area of targeted therapies, but mainly concerned classical chemotherapies (cisplatin and 5-fluorouracil). The present review highlights some limits. Indeed, methodology seems not optimised and could be based on more accurate methods of dose-escalation.

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The present portrait of phase I radiochemotherapy trials suggests that radiochemotherapy notion must be reinvented and trials should be adapted to its complexity. Step by step method does not sound like an option anymore. Let us build the future of radiochemotherapy on past evidences.

1. Introduction

In the ideal setting, radiochemotherapy (RC) follows the equation 1 + 1 = 3, with a synergistic effect: RC allows spatial cooperation (radiotherapy [RT] acts locally while anticancer drugs have a systemic action) and enhances tumour cell sensitivity to RT with radio-sensitising effects. Thus, numerous trials have demonstrated that RC is able to improve local control, overall survival, and decreases distant metastasis [1–3]. Nonetheless, this combination can induce some high-grade acute and late toxicity [4–7], and recall reactions (which come out as acute effects but occurring several weeks to months after irradiation). Phase I clinical studies are designed to assess related-to-RC toxicities and only allow the development of combination with favourable efficacy/toxicity ratio. Indeed, the main objective of phase I trials in oncology is to determine the recommended phase II dose (RP2D), without exposing the included patients to sub therapeutic or toxic doses [8]. Essential items should be reported to analyse the experimental design of a phase I study, and to determine RP2D: inclusion and exclusion criteria, initial dose rational, number of different doses levels, number of needed patients for each level, dose escalation method, treatment, primary end-point, adverse events [9], dose limiting toxicity (DLT), and stopping rules definitions. Different schemes of dose-escalation have been developed to determine the maximum tolerated dose (MTD) and RP2D: Rule-based designs are the most used in phase I oncology trials [10,11], in particular '3 + 3' design and its variations. Model-based designs as continual reassessment method (CRM) are less used, mainly because they require more elaborated calculation methods, with difficulties of real-time implementation [12,13]. Phase I trials studying the concomitant association of RT with anticancer treatments raise specific problems. Firstly, the anticancer agent MTD may vary if associated with RT. Secondly, patients in RC trials are often included with locally advanced cancers, while trials evaluating a single anticancer treatment include most often metastatic and refractory to standard therapies patients [14]. Therefore, the toxicity reporting and design description should be particularly rigorous in RC trials.

To our knowledge, there is no exhaustive literature review describing the essential characteristics of early phase RC trials.

The objective of the present study was to describe and analyse early RC clinical trials reported in the last three decades.

2. Methods

Requests were performed in the Medline database (*via* PubMed) to identify all publications of early phase trials analysing concomitant chemoradiotherapy or the association of radiation therapy with a concurrent non-cytotoxic agent (NCA). The latest update was performed in June 2015, using the following MESH terms: 'clinical trials, phase I as topic', 'chemoradiotherapy', 'humans', as keywords and 'English' as limit. Using this only database of course induces a selection bias.

2.1. Study selection

Phase I and/or phase I/II trials were eligible for inclusion if chemotherapies and/or NCAs were administered concomitantly to radiation therapy. Exclusion criteria were: concomitant immunotherapy trials, phase I/II trials with no detail on the experimental design of the phase I part, phase II trials, phase I trials using sequential chemoradiotherapy, and sole abstracts. In case of several publications for the same trial, only most recent data were considered. A first selection was conducted based on title and abstract. Then eligible articles were selected on full text and reviewed. Selections were carried out independently by two reviewers. Concordant articles were included in analysis by the first reviewer and disagreements between the two selections were resolved by a third reviewer.

2.2. Data collection

For each selected trial, two different reviewers collected the following data: journal's name, year of publication, rational (presence/absence), number of participating centres (mono/multicenter study), number of included patients, cancer(s) studied, type of trial (phase I, phase I/II), mathematic model of dose-escalation (rule-based method or model-based method), RT fractionation, RT technique, RT dose escalation (yes/no), concurrent chemotherapy (CT) administration (yes/no), cytotoxic agents' name, CT dose escalation (yes/no), concurrent NCA administration (yes/no), NCAs' name, NCA dose