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Life-expectancy of patients enrolled in phase 1 clinical trials: A systematic review of published prognostic models

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Contents

Abstract

Life-expectancy superior to 3 months is a key-eligibility criterion for contemporary oncology phase 1 trials. Nevertheless, there is no reliable and consensual guidance for estimating this criterion. We have conducted a systematic review of published studies investigating the risk factor for 90-day mortality and the inherent generated scores. Nine studies have been published on this topic. Only two of these prognostic models have been validated on an independent dataset. Most of the models are based on a very subjective and investigator-dependent parameter: the performance status. The predictive performance of these prognostic models is poorly evaluated.

Keywords: Life-expectancy; Survival; Prognostic models; Prognostic Factors; Phase 1 clinical trial

1. Introduction

For decades, during the classical cytotoxic agents area, the major objectives of dose-seeking phase I studies were: to determine the relationship between the toxicity and dose-schedule of treatment for a given drug, to explore the

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pharmacodynamic/pharmacokinetic parameters, and finally to estimate the maximum tolerated dose (MTD) and then the recommended phase II dose [1]. Today, the development of molecular targeted agents needs to refine some of these simple and straightforward concepts and then shift to more sophisticated ones such as identification of optimal biological dose rather than MTD, selection of enriched populations expressing the target or the activated pathway(s), long-term toxicity assessment periods [2–9].

Whatever their intrinsic differences, the dose-seeking phase 1 exploring classical cytotoxic agents as well as molecular targeted therapies require a sufficient life-expectancy, usually a "life-expectancy of more than 3-month" [10–12]. The reasons why this eligibility criterion is required are numerous. First of all, from ethical and medical points of view, it is not acceptable to expose ultimately ill patients to potentially toxic treatment. Moreover, this sufficient life-expectancy allows a reliable exploration of the safety profile, the drug activity and the pharmacodynamic/pharmacokinetic parameters. The inclusion of patients with sufficient life-expectancy permist, in most cases, to discriminate the symptoms related to the tumor and the toxicity related to the new drug. Selecting patients with sufficient life-expectancy is of major importance to reduce the duration of the study by limiting the number of patients having to be replaced. This particular eligibility criterion is crucial for patient safety and for the proper conduct of the study [14–16]. Regarding these facts, several institutions or academic groups have recently developed prognostic scores or models to guide the investigators in appropriately selecting patients for phase 1 trials. We propose herein to review these models.

2. Materials and methods

Pubmed was searched using the following key-words "phase 1 clinical trial" AND "prognostic factors", the following limits "humans", "English language" and terms used in the "title/abstract". We have excluded congress presentations without definitive issued articles. Two hundred and fifteen articles were preselected (1966 to November 2009). From these 215 articles, we have excluded (i) the articles without survival data, (ii) the articles reporting phase II or phase III trials and (ii) the report of single phase I trial(s) and (iv) reports of studies enrolling non-cancer patients.

At the end, only 9 studies have been selected for the systematic review.

Methods used to identify prognostic factors, primary endpoint (overall survival, 90-day mortality...) and the prognostic factors identified were collected from these 9 publications. For each proposed model, the methodology used to construct the model was described together with the methods used for validation, if applicable.

3. Results

3.1. Studies populations

Prognostic factors were identified in 9 publications. Eight studies were single-center whereas one was multicentric (Table 1). Sample sizes were, in most studies, limited, ranging from 82 to 420 patients. Medical charts were collected over various time periods, ranging from one [10] to 9 years [13,23]. The most ancient cases were treated in 1986 and the most recent ones in 2007. Fifty six percent of study participant were males and the median age ranged from 54 [18,19] to 60 [17]. In most cases, the study population consisted of patients with various solid tumors. In one study, all patients had lung cancers [17] and in one study, 4% of patients had hematological malignancies [11]. The majority of patients (72–99%) had good performance status (PS = 0 or 1). In seven studies, investigational agents were classical cytotoxic agents or molecular targeted therapies. Two studies focused on patients receiving exclusively cytotoxic chemotherapy [19,23].

3.2. Primary endpoint and univariate analysis

The primary endpoint of 7 studies was overall survival. The primary endpoint of the 2 others studies was the 90-day mortality [20,23]. As a consequence, univariate analyses used log-rank test in 7 studies and chi-square tests or univariate logistic regression in 2 studies [20,23] (Table 2).

3.3. Identification of prognostic factors by multivariate analyses

Depending on the nature of the primary endpoint (overall survival versus 90-day mortality), multivariate analyses used Cox model analyses in 7 cases [10,11,13,17–19,22] and multivariate logistic regression in 2 cases [20,23] (Table 2). Authors found between 2 [18,19,23] and 5 independent prognostic factors [11,13]. The following prognostic factors were frequently retained by multivariate analysis: albumin (5 studies) [10,11,19,20,23], ECOG (5 studies) [11,13,17,18,20], number of metastastic sites (4 studies) [10,13,17,20], LDH (4 studies) [10,13,18,20], white cell count (2 studies) [13,20] and lymphocytes count (2 studies) [19,23]. On the contrary, 6 factors were retained by the multivariate analysis in only one study (Table 3) [10,11,13,17–20,22,23].

3.4. Development of prognostic models

All authors but Arkenau et al. proposed new prognostic models [10,11,13,17–19,22,23]. In all cases, the methodology used to create subgroups was not precisely described and the scores were basically the sum of the number of prognostic factors identified for each patient, whatever the statistical weight of each of these prognostic factors. In the end, patients were classified into 2 or 3 groups depending of the number of prognostic factors (Table 4). On the contrary, Arkenau et al.