European Journal of Cancer (2015) 51, 2501–2507

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Correlation of single arm versus randomised phase 2 oncology trial characteristics with phase 3 outcome

Jose G. Monzon [a,*,1], Annette E. Hay [b,1], Gail T. McDonald [b], Joseph L. Pater [b], Ralph M. Meyer [c], Eric Chen [d], Bingshu E. Chen [b], Janet E. Dancey [b]

[a] *Department of Medical Oncology, Tom Baker Cancer Centre, Calgary, Canada*
[b] *NCIC Clinical Trials Group, Queen's University, Kingston, Canada*
[c] *Department of Oncology, Juravinski Hospital and Cancer Centre and McMaster University, 711 Concession St., Hamilton, Ontario L8V 1C3, Canada*
[d] *Department of Medical Oncology, Princess Margaret Cancer Centre, Toronto, Canada*

Received 29 May 2015; received in revised form 3 August 2015; accepted 9 August 2015
Available online 31 August 2015

KEYWORDS
Single-arm
Randomised
Phase 2
Clinical trials

Abstract ***Background and aim:*** The primary aim of this study was to determine whether randomised phase 2 (RP2) trials predict phase 3 trial outcome better than single arm phase 2 (SAP2) studies. Although theoretical superiority of RP2 trials has been postulated, no empiric studies have been conducted.

Methods: Published phase 3 trials testing systemic cancer therapy were identified through a Medline search. Those of superiority design, which cited phase 2 trials supporting the experimental arm, were included. Trial design and outcome details were extracted. Statistical analysis was performed using the Generalized Estimating Equation method correlating phase 2 features with phase 3 outcome, accounting for any phase 3 duplication.

Results: Of 189 eligible phase 3 trials, 18.5% were in haematological malignancies and 81.5% in solid tumors. The primary outcome was positive in 79 (41.8%). These were supported by 336 phase 2 trials (range 1–9 per phase 3 trial) including 66 RP2 trials. Positive phase 2 outcome, randomised or not, correlated with positive phase 3 outcome ($p = 0.03$). RP2 studies were not superior to SAP2 studies at predicting phase 3 study success. Phase 2 trial features not predictive of phase 3 outcome included primary endpoint, sponsorship, sample size, similarity in patient population and therapy.

Conclusions: RP2 studies were not superior to SAP2 trials at predicting phase 3 study success. Further research into phase 2 trial design is required given the added resources required to

* Corresponding author at: FRCPC, Department of Medical Oncology, Tom Baker Cancer Centre, Calgary, Alberta T2N 1E1, Canada. Tel.: +1 403 521 3196; fax: +1 403 283 1651.
E-mail address: jose.monzon@albertahealthservices.ca (J.G. Monzon).
[1] Both authors contributed equally.

http://dx.doi.org/10.1016/j.ejca.2015.08.004

conduct RP2 studies and the lack of empiric evidence supporting superiority over single arm studies.

1. Introduction

The oncology drug development process is inefficient, with an attrition rate for novel cancer drugs ranging from 74–95% [1,2]. This translates to one in four to one in 20 clinically evaluated oncological drugs gaining regulatory approval. As approved oncology drugs must bear the costs of developing drugs that fail, the estimated cost of successfully developing an oncology drug is reported to range from 0.8 to 1 billion US dollars [2–4]. This cost is overshadowed by the social and financial costs of the tens to hundreds of thousand life-years lost while patients wait for the development of effective therapies, typically taking over a decade from preclinical testing to approval [5]. This highlights the importance of gathering reliable safety and efficacy data prior to initiating phase 3 (P3) studies. The most common strategy is to evaluate a new drug in a phase 2 (P2) trial prior to proceeding with P3 studies.

The goal of P2 trials is to obtain estimates of drug efficacy in a given cancer type while gathering additional safety data. Historically, these trials were single arm in design with the objective response rate (RR) as the most common primary/co-primary endpoint [6]. As single arm P2 (SAP2) trial outcomes are interpreted relative to historical controls, they are subject to selection bias and other potential confounding factors. Increasingly, randomised P2 (RP2) trials are conducted to minimise these biases especially in the context of more clinically relevant time to event endpoints. As a result, there is a presumption that RP2 studies are superior to SAP2 studies at predicting the outcome of P3 trials [7–9].

Statistical modelling studies using computer generated and individual patient trial data demonstrated that SAP2 trials were 2–4-fold more likely to experience type 1 error (false positive) and had less predictive power than RP2 designs [10,11]. We sought to determine if RP2 studies were superior to SAP2 trials at predicting P3 outcomes. We also attempted to identify P2 study characteristics that best predict for P3 outcome.

2. Methods

2.1. Literature search

P3 randomised controlled trials were identified in a MEDLINE search using the key words, 'cancer', 'randomiz* clinical trial', 'phase 3', and 'phase III' and explosion of the terms 'clinical trials' and 'neoplasm.' The search was limited to articles published between 1st January 2007 and 20th September 2012 in the highest impact factor journals publishing clinical trials (*Annals of Oncology*, *Blood*, *British Journal of Cancer*, *British Journal of Haematology*, *Cancer*, *European Journal of Cancer*, *Clinical Cancer Research*, *Haematologica*, *Journal of the American Medical Association*, *Journal of Clinical Oncology*, *International Journal of Cancer*, *Journal of the National Cancer Institute*, *Lancet*, *Lancet Oncology*, *Leukemia*, and the *New England Journal of Medicine*).

2.2. Phase 3 study selection

P3 trials identified in the Medline search were reviewed to select those meeting inclusion criteria for this analysis. Trials designed to detect superiority of a systemic cancer drug or combinations in adults were eligible. Excluded were meta-analyses, pooled data analyses, secondary analyses of previously published studies and trials solely testing radiotherapy, surgical, supportive care, transplantation or preventative interventions. P3 trials that had fewer than 100 patients per arm, did not cite P2 studies, or compared different doses or schedules of the same agent(s) were also excluded (see Fig. 1).

2.3. Phase 2 study selection

The P2 trial(s) justifying the testing and trial design of agents used in the experimental arm of P3 trials were obtained from the P3 trial citations. Single agents tested in the P2 setting that were subsequently tested in combination in the P3 setting were included. P2 drug combinations needed to match those used in the P3 settings, although dose or schedule could have been modified. If a P2 trial included exactly the same combination as tested in the P3 study, any additional P2 trials looking at single agents only were excluded.

2.4. Data collection

Data were extracted by two of three reviewers (A.E. Hay, G. McDonald, or J.G. Monzon). The third investigator adjudicated any discrepancies. Characteristics extracted from both the P2 and P3 trials were publication year, journal, declared continent of first author, funding, cooperative group trials, tumour type, treatment type and setting. Data collected included sample size, number of arms, presence of blinding, independent