European Journal of Cancer 66 (2016) 95–103

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Early change in tumour size predicts overall survival in patients with first-line metastatic breast cancer

Sonya C. Tate [a,*], Valerie Andre [b], Nathan Enas [c], Benjamin Ribba [d], Ivelina Gueorguieva [a]

[a] PK/PD, Eli Lilly and Company, Erl Wood Manor, Windlesham, GU20 6PH, UK
[b] Statistics, Eli Lilly and Company, Erl Wood Manor, Windlesham, GU20 6PH, UK
[c] Statistics, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA
[d] Project-Team NuMed, INRIA, Ecole Normale Supérieure de Lyon, Lyon, France

Received 12 November 2015; received in revised form 8 July 2016; accepted 8 July 2016

KEYWORDS
Survival analysis;
Breast cancer;
Gemcitabine;
Paclitaxel;
Docetaxel;
Capecitabine;
Mathematical model;
Treatment outcome;
Response evaluation criteria in solid tumours

Abstract ***Purpose:*** Clinical trials using change in tumour size (CTS) as a primary end-point benefit from earlier evaluation of treatment effect and increased study power over progression-free survival, ultimately resulting in more timely regulatory approvals for cancer patients. In this work, a modelling framework was established to further characterise the relationship between CTS and overall survival (OS) in first-line metastatic breast cancer (mBC).
Methods: Data from three randomised phase III trials designed to evaluate the clinical benefit of gemcitabine combination therapy in mBC patients were collated. Two drug-dependent models were developed to describe tumour growth dynamics: the first for paclitaxel/gemcitabine treatment and the second for docetaxel/gemcitabine treatment. A parametric survival model was used to characterise survival as a function of CTS and baseline patient demographics.
Results: While the paclitaxel/gemcitabine model incorporated tumour shrinkage by both paclitaxel and gemcitabine with resistance to paclitaxel, the docetaxel/gemcitabine model incorporated shrinkage and resistance to docetaxel alone. Predictors for OS were CTS at week 8, baseline tumour size and ECOG performance status. Model predictions reveal that for an asymptomatic mBC patient with a 6-cm tumour burden, first-line paclitaxel/gemcitabine treatment offers a median OS of 28.6 months, compared to 26.0 months for paclitaxel alone.

* *Corresponding author.*
E-mail addresses: tate_sonya@network.lilly.com (S.C. Tate), andre_valerie@lilly.com (V. Andre), enas_nathan_h@lilly.com (N. Enas), benjamin.ribba@inria.fr (B. Ribba), gueorguieva_ivelina@lilly.com (I. Gueorguieva).

http://dx.doi.org/10.1016/j.ejca.2016.07.009

Conclusion: A modelling framework was established, quantitatively describing the tumour growth inhibitory effects of various gemcitabine combotherapies and the effect of the resulting CTS on survival in first-line mBC. This work further supports the use of early CTS as a go/no-go decision point during phase II clinical evaluation of treatments for mBC.

1. Introduction

Breast cancer is the most commonly diagnosed malignancy in US [1] and European [2] women, forming an estimated 29% of new cancer cases in 2012–2013 [1,2]. Although early diagnosis offers the best chance for survival, those presenting with distant metastases have a poorer prognosis [1]. However, despite the need for new treatments, almost two-thirds of oncology drugs entering phase III clinical trials are terminated prior to registration [3], often due to lack of efficacy [3,4]. This represents failure to improve survival rates for metastatic breast cancer (mBC) patients and severely limits the resources available to develop new treatments. By improving go/no-go decision making prior to initiation of high-cost phase III clinical trials, resources can be focused on making efficacious therapies available to mBC patients in a more timely manner.

To best evaluate the potential benefit of a cancer treatment in early clinical testing, investigators would ideally understand how results from a phase II clinical trial might relate to the outcome of a large-scale registration trial. Change in tumour size (CTS) after 6–8 weeks of treatment has been related to overall survival (OS) for a number of malignancies, including colorectal [5], thyroid [6] and NSCLC [7] and may offer an opportunity for early evaluation of potential clinical benefit [5,7]. Of particular note, Claret *et al.* [5] demonstrated the predictive utility of a drug-disease modelling framework for colorectal cancer, successfully predicting the outcome of a phase III trial from CTS in phase II. Phase II trials which employ CTS as a primary end-point may therefore provide early evaluation of treatment effect (with fewer patients [8,9]), thereby allowing decision makers to select the most promising candidates to be advanced to registration trials and ultimately resulting in more timely regulatory approvals for cancer patients.

As the relationship between CTS and OS is specific to the target treatment population, survival models incorporating CTS have to be developed for each tumour type of interest and line of treatment [7]. While a survival model was previously developed for mBC patients [10], the model was not specific for first-line treatment and did not fully assess the optimum CTS timepoint for correlation to survival. In this study, three phase III clinical trials were used to (1) quantify the antitumour effect of paclitaxel, paclitaxel/gemcitabine, docetaxel/capecitabine and docetaxel/gemcitabine in first-line mBC and (2) establish and quantify early predictors of OS. The predictive potential of the resulting tumour growth inhibition and survival modelling framework for mBC was demonstrated.

2. Patients and methods

2.1. Clinical trial selection

Three randomised clinical trials for mBC were selected based on available in-house longitudinal tumour size and survival data. Study JHQG (NCT00006459) [11] compared paclitaxel with paclitaxel/gemcitabine therapy, while studies S273 (NCT00191152) [12] and S188 (NCT00191438) [13] evaluated the benefits of docetaxel combined with either capecitabine or gemcitabine.

All three clinical studies were conducted in accordance with the Declaration of Helsinki and were approved by the Investigational Review Board. Written informed consent was obtained from all patients. Study methodologies and results are described in detail elsewhere [11–13].

2.2. Tumour size dataset inclusion criteria

Radiologic assessments were performed in all three clinical trials. In JHQG, treatment response was evaluated using the WHO [14] criteria, with radiological measurement of tumour sizes scheduled to occur every 8 ± 1 weeks. In S188 and S273, treatment response was evaluated using RECIST 1.0 [15], with tumour size assessment scheduled to occur after every three cycles of treatment; confirmation scans were performed after 3–4 weeks of first response.

As RECIST represents the standard method of treatment response assessment in mBC trials, the JHQG tumour size data were aligned to RECIST 1.0 using the following inclusion criteria:

1. Only include lesions present at first evaluation.
2. Minimum lesion diameter of 0.5 cm.
3. Only include lesions measured by computed tomography scan.
4. Tumour size computed as the sum of longest diameters.

For consistency, the same limit of quantification was applied to S188 and S273. As the focus of the present