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Original article

More than just the median: Calculating survival times for patients with HER2 positive, metastatic breast cancer using data from recent randomised trials

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ABSTRACT

Objectives: To estimate worst-case, typical and best-case scenarios for survival as a communication aid for managing patients with HER2-positive metastatic breast cancer (MBC) starting HER2-targeted therapies.

Methods: We sought randomised trials of HER2-targeted therapies and recorded the following percentiles (representative scenarios) from each OS curve: 90th (worst-case), 75th (lower-typical), 50th (median), 25th (upper-typical) and 10th (best-case). We then tested whether we could estimate these percentiles for each OS curve by multiplying its median by four simple multiples: 0.25 (to derive the 90th percentile), 0.5 (75th), 2 (25th) and 3 (10th). Estimates were deemed accurate if within 0.75–1.33 times the actual value.

Results: We identified 15 trials with 4798 patients. For first-line, single-agent HER2-targeted therapy (15 treatment groups), the median (interquartile range [IQR]) for median OS was 33.3 months (29.1–38.4), and for each percentile was: 90th 9.5 months (7.7–11.0); 75th 19.2 months (16.4–20.8); and 25th 50.6 months (47.1–63.3). The 10th percentile was unavailable for all treatment groups. For first-line dual HER2-targeted therapy (1 treatment group), the median OS was 56.5 months. Simple multiples of the median OS accurately estimated the: 90th percentile in 79%; 75th percentile in 100%; and 25th percentile in 89% of OS curves.

Conclusions: Surprisingly little is known of survival beyond the median for HER2-positive MBC. Longer trial follow-up is required to help clinicians estimate and explain the best-case scenario. Simple multiples of the median OS provide a reasonable framework for estimating then explaining survival times to patients.

Introduction

Metastatic breast cancer (MBC) is a heterogeneous disease with highly variable outcomes depending on multiple cancer, patient and treatment factors. HER2 positive MBC is characterised by a more aggressive course with a higher mortality rate and shortened survival time [1]. HER2-targeted therapy has significantly improved the outlook of HER2 positive MBC. Trastuzumab has been the mainstay of treatment for almost a decade; however, the development of newer HER2-targeted therapies in recent years has provided further treatment options and consequently improved survival times in these patients.

Oncologists are frequently required to estimate and explain survival time to women with MBC. In previous work we proposed that estimating and explaining three scenarios for survival time – worst-case, typical, and best-case – conveys more meaning and hope than explaining a single point estimate of the median overall survival (OS) [2,3]. The percentiles of an OS curve are a useful basis for estimating these scenarios [4]. We summarised the survival times of patients starting chemotherapy for advanced breast cancer, non-small-cell lung cancer and prostate cancer and found that the survival curves were approximately

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exponential in shape allowing the percentiles of each OS curve to be estimated by simple multiples of its median [5–7]. For example, the 90th percentile (representing the upper bound for the worst-case scenario) was approximately one-quarter of the median OS, the 75th percentile (lower bound of the typical scenario) was half the median OS, the 25th percentile (upper bound of the typical scenario) was double the median OS and the 10th percentile (lower bound of the best-case scenario) was three times the median OS [5–7]. These simple rules provide a useful framework for oncologists when estimating and explaining survival time to patients with advanced cancers starting chemotherapy. For example, an oncologist who estimates a patient's survival as 12 months could say "the typical survival for people in your situation is between 6 months and 2 years" (between half and double the median).

With the availability of new and effective HER2-targeted therapies, the survival times for patients with HER2 positive MBC are considerably longer than those for patients with HER2 negative MBC starting chemotherapy. The purpose of this study was to find and summarise survival data from recent randomised trials of HER2-targeted therapies for HER2 positive MBC to help oncologists more accurately estimate scenarios for survival time for their patients in this situation. We also sought to determine if the same simple multiples of the median OS that were accurate for estimating the bounds of worst-case, typical and best-case scenarios for survival in chemotherapy trials were accurate in these trials of HER2-targeted therapies.

Methods

We searched the Cochrane Database of Systematic Reviews, Medline and the ASCO meeting library for trials published or presented between 2001 and 2015. We used the keywords: "HER2 positive" and "metastatic breast cancer". The reference list from a recently published systematic review of HER2 positive, MBC was used to supplement the results from this search [8].

References were deemed eligible if they met the following eligibility criteria: randomised trial; participants with HER2 positive MBC; at least 90 participants in each treatment group; at least one treatment group with HER2-targeted therapy (given alone or combined with chemotherapy or endocrine therapy); and included a Kaplan–Meier curve for OS. Although arbitrary, the decision to exclude trials with less than 90 participants per treatment group was in keeping with our other work [5–7], and should ensure sufficient precision of survival estimates at longer follow-up times.

We recorded the following data from each trial: year of publication, treatment regimen, number of participants, median follow-up, patient demographics and tumour characteristics. We also recorded median progression free survival (PFS) and median OS for each treatment group and extracted the OS curve from each trial. We categorised the trials according to whether the HER2-targeted therapy was first-line or subsequent-line, and whether there was single or dual agent HER2-targeted therapy.

Two authors independently traced each OS curve using the UNSCAN-IT graph digitising software [9]. The following percentiles (represented scenarios) were extracted from each OS curve: 90th (worst-case), 75th (lower-typical), 25th (upper-typical), and 10th (best-case) (Fig. 1). Inconsistencies were resolved by repeated measurement, discussion, and consensus.

On the basis of our previous work in chemotherapy trials [5–7], we hypothesised that multiplying each OS curve's median by four simple multiples would allow us to estimate its percentiles (representative scenarios) as follows: 0.25 for the 90th percentile (worst-case), 0.5 for the 75th percentile (lower-typical), 2 for the 25th percentile (upper-typical) and 3 for the 10th percentile (best-case). As in our previous work, we deemed each estimate accurate if it was within 0.75–1.33 times the actual value [5–7]. Based on our findings in the MBC review [5] we also hypothesised that for each treatment group the median OS would be approximately three times the median PFS (ratio 3:1).

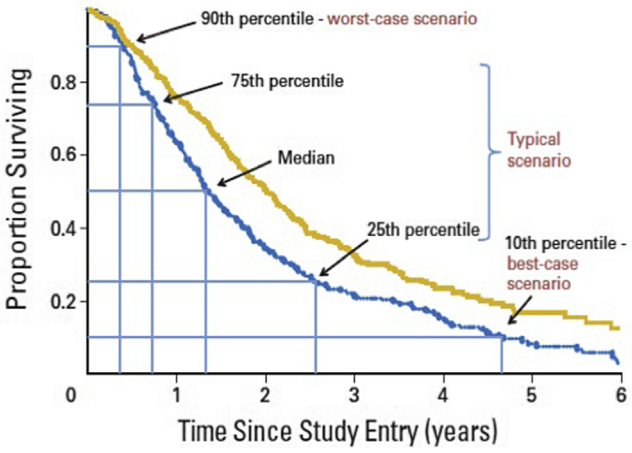

Fig. 1. Kaplan–Meier OS curve percentiles and their corresponding scenarios.

Linear regression weighted for the number of participants in each trial was used to assess associations between the following first-line trial characteristics and median OS: year of publication, number of HER2-targeted therapies, number of chemotherapy agents, use of a taxane, median age of participants, percentage of participants who had received adjuvant chemotherapy, percentage who had received adjuvant trastuzumab, percentage with ER/PR positive tumours and percentage of participants with visceral metastases and brain metastases.

Results

Our search strategy identified 73 references, of which 39 were duplicates of the same study, 14 did not have an OS curve, one included only HER2 negative patients, and 4 had less than 90 participants per treatment group. The 15 eligible trials included 24 treatment groups of the following HER2-targeted therapies: trastuzumab (13), lapatinib (6), trastuzumab-emtansine (TDM-1) (2), trastuzumab and pertuzumab (1), trastuzumab and lapatinib (1) and neratinib (1).

There were 10 first-line trials including 2676 participants receiving HER2-targeted therapies in 16 treatment groups [10–19]. There were 5 subsequent-line trials including 2122 participants receiving HER2-targeted therapies in 8 treatment groups [20–24]. Trial characteristics are summarised in Table 1. Median follow-up for the first-line trials was 35 months, (range 22–50 months) and for the subsequent-line trials was 15 months, (range 7–19 months). Follow-up was insufficient to report on the median OS in one treatment group (4%), the 25th percentile in 15 treatment groups (62%), and the 10th percentile in all 24 treatment groups.

All participants were HER2 positive, defined as FISH (fluorescent in-situ hybridisation) positive or IHC (immunohistochemistry) 3+. Approximately half of the participants had received adjuvant chemotherapy and half had received prior endocrine therapy. Few participants had received adjuvant trastuzumab – 88 (3.2%) in the first-line setting (all were enrolled in the CLEOPATRA trial [11]) and 89 (4.2%) in the subsequent-line setting. The presence of brain metastases was only reported in 8 of the 15 trials, with no participants in the first-line setting and 35 participants