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Estimating scenarios for survival time in men starting systemic therapies for castration-resistant prostate cancer: A systematic review of randomised trials ☆

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Abstract ***Background:*** We sought to estimate worst-case, typical and best-case scenarios for survival in men starting systemic therapies for castration resistant prostate cancer (CRPC). ***Methods:*** We sought randomised phase 3 trials of systemic therapies for CRPC and recorded the following percentiles (represented scenario) from Kaplan–Meier overall survival (OS) curves: 90th (worst-case), 75th (lower-typical), 50th (median), 25th (upper-typical) and 10th (best-case). We determined the accuracy of using simple multiples of the median OS to estimate the other selected percentiles from each curve: 0.25 for 90th, 0.5 for 75th, 2 for 25th and 3 for 10th. Estimates were deemed accurate if within 0.75–1.33 times the actual value. ***Findings:*** We reviewed 23 trials (13,909 men) with 48 treatment groups including 28 of chemotherapy, and three of novel hormonal agents. In trials of first-line docetaxel, the mean (interquartile range) for median OS was 19 months (17–20), and for each scenario was: worst-case 7 months (6–8); lower-typical 12 months (11–13); upper-typical 29 months (27–31); and best-case 40 months (34–44). For trials of novel hormonal agents after chemotherapy the mean values were: median OS 17 months, worst-case 5 months, lower-typical 9 months, upper-typical 24 months and best-case not reported. Simple multiples of the median gave accurate estimates of the worst-case scenario in 72% of OS curves, lower-typical in 89%, upper-typical in 84% and best-case in 84%.

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Interpretation: Simple multiples of the median OS from randomised trials provided accurate estimates of worst-case, typical and best-case scenarios for survival time in men starting systemic therapies for CRPC.

1. Introduction

Castration-resistant prostate cancer (CRPC) occurs in 10–20% of those diagnosed with prostate cancer, the second most common cancer and sixth most common cause of cancer death in men [1,2]. Chemotherapy with docetaxel has been the standard of care for metastatic CRPC following its approval by the US FDA in May 2004, but a panoply of new treatments has subsequently become available, five of which have been shown to improve overall survival (OS) [3]. Clinicians caring for men with CRPC are currently facing the challenge of how best to explain and sequence these new therapies to maximise their net benefits.

Surveys of patients with advanced cancer have found that the majority want quantitative information about their likely survival time, including best-case and worst-case scenarios, and that prognostic information should be honest but also convey hope [4–6]. Despite these findings, doctors rarely provide patients with quantitative estimates of survival time, talk about prognosis less than other aspects of the disease and frequently avoid the subject entirely [5,6]. Furthermore, when prognostic information is provided, patients frequently misunderstand it [5,7].

We have previously shown that selected percentiles of an OS curve can be used to estimate and explain worst-case, typical and best-case scenarios for survival time: the 90th percentile (the maximum survival time in the 10% of patients living the shortest) to reflect a worst-case scenario, the 75th to 25th percentiles (the middle 50% of survival times) to reflect a typical scenario and the 10th percentile (the minimum survival time in the 10% of patients living the longest) to reflect a best-case scenario [8]. In systematic reviews of first-line chemotherapy trials for advanced non-small cell lung cancer (NSCLC) and metastatic breast cancer (MBC), we found that simple multiples of each OS curve's median could be used to estimate its percentiles corresponding to these scenarios for survival [9,10]. The worst-case scenario could be estimated as one-quarter of the median OS, the typical scenario as half to double the median OS, and the best-case scenario as three times the median. In related work, we have demonstrated that patients find survival information presented as three scenarios easier to understand, reassuring and preferable to receiving a single estimate of the median survival [11].

The purpose of the current study was to find and summarise survival data from recent randomised trials of systemic therapy in CRPC. We also sought to determine the accuracy of using simple multiples of the median OS to estimate worst-case, typical and best-case scenarios for survival. Such information is intended to help clinicians better estimate and explain survival time in men starting such treatments for CRPC.

2. Methods

We searched MEDLINE for randomised trials of systemic therapy for CRPC. Search terms included the headings 'prostatic neoplasms', 'drug therapy', 'antineoplastic agents', 'antimitotic agents' and heading and text-word searches for the generic and brand names of pharmacological agents listed in recent reviews of prostate cancer [3,12,13].

One author conducted the initial search and filtering, and two authors independently screened the references and selected trials meeting the following inclusion criteria: randomised phase 3 trial of systemic therapy for men with CRPC including at least 80 patients enrolled per treatment arm, and a Kaplan–Meier curve for OS. Trials evaluating bone directed therapies were excluded. Trials were classified as either first-line therapy (i.e. no previous cytotoxic chemotherapy) or second-line therapy (i.e. following progression after one line of cytotoxic chemotherapy).

For each eligible trial, we recorded the journal and year of publication, the definition of castration-resistance, the median follow-up time and the number of treatment arms.

For each treatment arm, we recorded the names and schedules of the drug therapies, the numbers of patients and summary of data describing the baseline characteristics of the included patients, tumours, biochemical markers and previous treatments.

Each OS curve was independently traced by two authors using UN-SCAN-IT graph digitising software [14]. The median and the following percentiles (representative scenario) were extracted from each curve: 90th (worst-case), 75th (lower-typical), 25th (upper-typical) and 10th (best-case). These percentiles are depicted in Fig. 1. The two authors' measurements were deemed to match if they were within 5% of each other; disagreements were resolved by repeated measurement and discussion. The measured median OS was also compared to the reported median OS to assess accuracy of measurements.