Evidence synthesis to accelerate and improve the evaluation of therapies for metastatic hormone-sensitive prostate cancer

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Word count: 2991 (including abstract)

Abstract:

There are many ongoing randomised trials of promising therapies for metastatic hormone sensitive prostate cancer (mHSPC), but standard systematic reviews may not synthesise these in a timely or reliable way.

We demonstrate how a novel approach to evidence synthesis is being used to speed up and improve treatment evaluations for mHSPC. This more prospective, dynamic and collaborative approach to systematic reviews of both trial results and individual participant data (IPD) is helping to establish quickly and reliably which treatments are most effective, and for which men.

However, mHSPC is a complex disease and trials can be lengthy. Thus, parallel efforts will synthesise further IPD to identify early surrogate endpoints for overall survival and prognostic factors, to reduce the duration of and improve the design of future trials. The STOPCAP M1 repository of IPD will be made available to other researchers for tackling new questions arising. The associated global, collaborative forum will aid strategic and harmonised development of the next generation of mHSPC trials (STOPCAP M1; http:\\www.stopcapm1.org).

Patient Summary: We report how our worldwide research effort will review results and anonymised data from advanced prostate cancer trials in new and different ways. We will work out, as quickly as possible, which advanced prostate cancer treatments are best and for which men. We will also find which measures of prostate cancer control and which cancer and patient characteristics can be used to shorten and improve trials of newer treatments. Finally, we describe how the data can help to answer new questions about advanced prostate cancer and its treatments.

Introduction

For decades, the treatment of metastatic, hormone-sensitive prostate cancer (mHSPC) was life-long androgen deprivation therapy (ADT), until the addition of either docetaxel or abiraterone to ADT was shown to substantially improve overall survival(1-5, 6). Further randomised trials, evaluating other promising therapies for this currently incurable disease, are expected to produce results in the coming years. Systematic reviews and meta-analyses are key tools for synthesising the evidence from such trials and defining the best therapies for patients, but most are retrospective and rely on published trial results. This means they can lag behind therapeutic developments, and the information they include may not be sufficient to ensure reliable findings. Also, trials in this setting are lengthy and mHSPC is a complex disease(7).

In this paper, we demonstrate how different evidence syntheses strategies are being used to speed up and improve the evaluation of treatments for mHSPC, and to inform and accelerate the conduct of future trials, which will allow men to have faster access to life-prolonging treatments. This international, coordinated and collaborative effort (STOPCAP M1; http:\\www.stopcapm1.org), will also provide a collaborative forum and foundation for harmonising the design, and strategically planning, the most important new trials in mHSPC.

Quickly and reliably determining the overall effects of treatments

Existing systematic review and meta-analysis approaches are not ideally suited to quickly and reliably synthesising emerging trial results and establishing the best therapies for mHSPC patients. Standardly, they are retrospective endeavours initiated when most or all relevant trials have already been published. Hence, their design and conduct may be influenced by knowledge of existing trial results, and inevitably, they will lag behind therapeutic developments. Also, most systematic reviews rely on published trials, and the results that those publications report, with unpublished and ongoing trials often being overlooked(8, 9). Although, this facilitates fairly quick completion of such reviews, they can be affected by multiple reporting biases(10), and may not include enough data to produce reliable and detailed findings. Further, it is difficult to place results in the context of all the potential trial evidence. By contrast, reviews based on individual participant data (IPD) from all relevant trials, patients and outcomes, can bring about substantial improvements to the quality of data and analyses, leading to much more robust and nuanced results with which to guide clinical practice(11, 12). However, whilst such IPD reviews are considered the gold standard(13), they are resource-intensive and can take many years to complete, such that reliable findings come much later than is needed by patients, clinicians and policy makers.

Therefore, a more prospectively-planned, dynamic and collaborative approach to systematic review, that integrates and makes the best use of firstly trial results and then IPD, is being employed to establish more quickly and reliably which treatments for mHSPC are most effective, and for whom. A key element of this has been the development of a new framework for adaptive meta-analysis (FAME)(14). has evolved into an entirely prospective approach to synthesising trial results (Figure 1), whereby the objectives, eligibility criteria, outcomes and analyses for the review are defined prior to all of trial results being available, lending the FAME approach a level of rigour more akin to a prospective trial. All eligible trials are sought whether published, unpublished or ongoing, and early engagement with trialists helps to generate a detailed picture of the accrual rates and completion

dates for ongoing trials, as well as anticipated reporting timelines for trials that have completed recruitment. With this knowledge, it is possible to predict the earliest opportunity for a reliable meta-analysis. This prediction is based on when trial anticipated trial results will likely represent a substantial proportion of the participants randomised across all relevant trials; provide sufficient power to detect realistic and clinically meaningful effects (14), and there being sufficient follow-up. This approach avoids waiting months or even years for trial results that are unlikely to contribute significantly to the meta-analysis, and at the same time, ensures that the meta-analysis results can be interpreted in the context of any unavailable data. In addition, the review planning can then be coordinated with trialists, to coincide and complement the emergence of keytrial results.

FAME has already been utilised to evaluate the effects of therapies for mHSPC (under the auspices of the STOPCAP M1 collaboration). For example, it has shown definitively that adding either docetaxel or abiraterone to ADT improves overall survival of men with mHSPC (5, 6), and that adding zoledronic acid does not(5), years ahead of all trial results being available (Figure 1). Importantly, collaboration with trial investigators facilitated access to pre-publication results, and to additional unpublished analyses of outcomes and subgroups, both speeding the review process up further and permitting a more thorough evaluation of benefits and harms than is usually possible with published data. For example, a FAME review highlighted that the improvement in survival seen with abiraterone is associated with increased serious acute side effects, but not an excess of deaths(6). Another showed that the benefit of prostate radiotherapy on survival in men with low metastatic burden is remarkably and reassuringly consistent across trials and outcomes (Eur Urol, under review), thereby serving to corroborate the results of the STAMPEDE trial (15) . Appropriate confidentiality agreements are put in place, to prevent premature disclosure of trial results by any of the parties, and the collaborative and coordinated approach allows reviews to be published in the same time frame as key trial results (Figure 1)., which seems to increase the visibility and impact of both The STOPCAP M1 collaboration will continue to use FAME to provide timely and reliable systematic reviews of other therapies, such as enzalutamide and other novel anti-androgens.

Assessing which treatments are most effective and for which men

Being based on trial results, FAME reviews are best suited to synthesising the overall effects of interventions, but there is a real need to ascertain reliably if some men with mHSPC attain greater benefit from effective treatments than others. Evidence from some trials suggests, for example, that the overall survival benefits associated with docetaxel and abiraterone vary according to the volume(16) or risk of disease(4). However, the trials used different definitions of disease burden, or had yet to collect the necessary data (2, 3). In addition, individual trials are rarely powered to detect such subgroup effects. Therefore, by collecting and re-analysing IPD from recently completed trials in mHSPC, it will be possible to assess whether any observed treatment effects vary according to pre-specified and consistently defined patient and tumour characteristics, using the most appropriate methodology (17, 18). Also, as in any meta-analysis, the power to identify such interactions will be greater than for an individual trial. Although the IPD approach is traditionally protracted, if the necessary collaborations have been established through FAME reviews then protocol development and data collection can proceed with minimum delay.

With the rapid evolution of the treatment paradigm for mHSPC comes the need to define the optimal strategies. However, many of the ongoing and recently completed trials have assessed the effects of new treatments relative to ADT alone, rather than the evolved standards of care, which

include docetaxel or abiraterone, and so there are limited head-to-head comparisons of effective treatments. In this scenario, network meta-analysis can be used to make optimal use of both the direct and indirect comparisons of treatments from all trials, and to allow the relative effects of all treatments to be ranked(19, 20). For example, a network meta-analysis that included the FAME reviews described above plus a trial of of celecoxib, generated a thorough overview of the effects of all current treatments (Figure 2), and provided substantial evidence that overall, abiraterone is the most effective treatment for mHSPC to date(21). However, this is in contrast to the results of a direct comparison of these agents based on a small subset of patients from the STAMPEDE trial(22). The collection of detailed IPD for a new network meta-analysis will provide an opportunity to investigate the likely causes of these different results, for example by accounting for the changing availability and use of effective treatments following progression during the life of the included trials, and incorporate both direct and indirect information in the most appropriate way. IPD will also help to appropriately deal with the complexities associated with inclusion of the PEACE-1 multi-arm trial (e.g. NCT01957436) and the adaptive STAMPEDE trial(23).

Speeding up the next generation of trials

Whilst the availability of new effective treatments will no doubt extend the lives of men with mHSPC, it also means that new trials that make use of overall survival as a primary outcome, will take longer than they do currently. Already such trials can take close to a decade to complete. Hence, there is widespread interest among clinical investigators, pharmaceutical companies, and regulatory agencies in employing surrogate endpoints that are available earlier in the course of the cancer's natural history, are measured more frequently, and are less costly than definitive endpoints, such as overall survival(24-26). The Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP M0) initiative has been successful in showing that metastases-free survival is a strong surrogate for overall survival, based on the synthesis of IPD from nearly 20 trials and 13,000 men with localized prostate cancer, independent of primary local therapy and the type of adjuvant therapy(27).

Building on the success of ICECAP M0, the STOPCAP M1 programme also includes a partner project that aims to identify potential surrogates for overall survival in mHSPC. It will investigate whether biochemical progression, time to castration-resistance and time to clinical progression are potential surrogates for overall survival. Demonstration of reliable surrogacy requires not only that an endpoint is correlated with overall survival, but also that treatment effect on the endpoint and overall survival are also correlated (Figure 3)(26, 28). This requires the collection and synthesis of IPD from multiple trials, incorporating a range of treatment effects. A cohort of 46 trials, conducted since the introduction of sensitive PSA-testing, but prior to evaluation of docetaxel, have been identified as eligible for the initial identification of surrogates, and include nearly 12, 000 men. Trialists supplying IPD will follow a detailed, pre-specified data dictionary, allowing patient and cancer characteristics, and all endpoints to be defined consistently across trials by the study team. Importantly, any strong surrogates identified can be re-validated based on similarly-detailed IPD from trials of newer therapies collected via the individual STOPCAP M1 systematic reviews of treatments.

Successful identification of intermediate clinical endpoints for overall survival will impact both the design (such as the choice of endpoint, sample size) and analysis of future mHSPC trials. Crucially, it could reduce trial duration, potentially by years, and moreover, decrease their cost. The ultimate

goal is to persuade the regulatory agencies globally, of the benefit of using strong, evidence-based and validated surrogate endpoints in new phase III trials in this setting. Demonstrating the validity of the surrogates on trials of newer therapies could be particularly persuasive, accelerating future trials and ultimately access to new potentially curative therapies for men who might otherwise die of their disease.

Improving patient selection and stratification in the next generation of trials

The literature on the identification and validation of prognostic factors of clinical outcomes in men with mHSPC is sparse(29, 30) such that, at present, most men with mHSPC receive the same treatment with varying clinical outcome. Most of the prognostic factors that have been identified can be related to either patient or tumor characteristics, such as PSA, Gleason sum score, and pain and performance status, but are they either based on outdated data(29), have not been validated(31) or the prognostic models lack discriminative ability(29, 30). In contrast, considerable resources have been dedicated to better understanding tumor heterogeneity and developing prognostic models of clinical outcomes in mCRPC(32-37).

Therefore, a further advantage of collecting detailed IPD through the STOPCAP M1 programme will be the ability to identify and validate prognostic factors in mHSPC. These factors could be used in defining eligible patients for future trials and to inform appropriate stratification factors for randomisation and analysis. Development of the prognostic models will follow the recently published American Joint Committee on Cancer and TRIPOD guidelines on model development and validation to ensure that rigorous tools will be produced(38-40). This more thorough understanding of the complex interactions between patient, tumor factors, and clinical outcomes will further influence the design of the next generation of clinical trials.

Harmonising the design of the next generation of trials

Interpretation of the impact of a new therapy on mHSPC outcomes and patient well-being requires use of precisely defined endpoints, which are reproducible, clinically meaningful and linked to the proposed mechanism of action of the intervention. Both individual endpoints (e.g. biological (PSA) progression) and composite endpoints (e.g. such as failure-free survival or progression-free survival) are commonly used in mHSPC trials to measure the impact of a new treatment or therapeutic strategy, but the definitions, particularly of the composites, are very inconsistent. For example, trials investigating the addition of docetaxel to ADT in mHSPC used different definitions of disease-free survival and failure-free survival(5). Harmonization of these and other endpoints between trials would enable clear interpretation of results of any specific analysis by stakeholders and equally important, allow comparisons between trials and facilitate the conduct of meta-analyses.

The COMET Initiative (www.comet-iniative.org) is an internationally recognized effort whose aim is to develop and apply standardised sets of outcomes, known as the 'core outcome set', for use in clinical trials and other forms of research. Using methods such as literature and systematic reviews, Delphi processes and consensus meetings, core outcome sets have already been generated in prostate cancer, for example, in the context of surgical management of localised prostate cancer(41). Beyond the COMET initiative, there are precedents of harmonization efforts for outcome reporting. A notable example in advanced prostate cancer is led by The Prostate Cancer-Specific Antigen Working Group which has generated recommendations for outcome reporting for patients

in the state of a rising prostate-specific antigen(42) and progressive prostate cancer and castrate levels of testosterone(43).

Linked to the need for harmonization of endpoints is the need to harmonize eligibility criteria. This pertains to the patient and disease characteristics, as well as methods used to measure endpoints. Ultrasensitive PSA assays and more recently, prostate specific membrane antigen based imaging are examples of methods of cancer detection and endpoint measurement that require standardization.

While the primary focus of the ICECaP M0 initiative has been to identify validated intermediate endpoints which are surrogates for overall survival in localised prostate cancer(27, 44), the consortium of experts brought together through the initiative have also been involved in efforts to develop standardized core eligibility and outcome sets for new therapeutic trials in early prostate cancer. A similar, worldwide collaboration of trialists and scientists and the data generated by the multiple projects comprising the STOPCAP M1 programme outlined here, will be well placed to drive parallel harmonisation efforts in mHSPC.

Discussion

A series of prospectively planned and collaborative systematic reviews have shown quickly and definitively that docetaxel, abiraterone and prostate radiotherapy are highly effective treatments for men for mHSPC. This same approach will be utilised to evaluate the effects of other promising adjuncts to ADT. The collection of IPD from all recent randomised trials conducted worldwide in men with mHSPC will help determine robustly and precisely which are the optimal treatments, and if some men benefit more than others. In addition, IPD will allow, for example, standardisation of data and analyses across trials, and provides greater scope and flexibility in the analyses particularly of time-to-event endpoints(11). It will also be used to identify surrogate outcomes and prognostic factors to reduce the duration and improve the conduct of future trials.

Across all the various projects, around 60 trials including more than 34,000 men are in the scope. Clearly then, gathering the IPD will require a coordinated, international, collaborative effort. However, it will also help to create the most detailed and clinically relevant IPD repository in mHSPC (STOPCAP M1 repository); one that will be updated as new trials become available. Thus, therapies, prognostic factors and surrogate outcomes can be re-evaluated as the treatment paradigm continues to evolve. Importantly, IPD from the repository will be made available to other researchers, to tackle new clinical and scientific questions that arise (subject to rigorous research proposals and appropriate data use agreements). Moreover, the various activities will bring together a large, global, collaborative forum and foundation for harmonising the design and strategically developing the next generation of mHSPC trials.

Acknowledgements

Such a large, ambitious and long-term programme, is only possible through the institutional support of the Medical Research Council Clinical Trials Unit at UCL, the Department of Biostatistics and Bioinformatics at Duke University and Cancer Clinical Trials division at Queen's Cancer Research Institute, and through dedicated grant funding from Prostate Cancer UK (Research Innovation

Award: RIA16-ST2-020) and the Prostate Cancer Foundation (Valor Challenge Award: 18CHALL02) for component projects.

Figure 1: The timelines of selected FAME systematic reviews in mHSPC

Figure 2: Direct and indirect comparisons of in a network meta-analysis of recent treatments for mHSPC

Figure 3: Correlation requirements for the identification and validation of intermediate clinical outcomes

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