Comment

Prostate radiotherapy for men with metastatic disease: a new comparison in the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial

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Introduction

Many patients presenting with metastatic prostate cancer ask whether they should have treatment to the prostate itself in addition to their hormone therapy. This question is increasingly common and there is a growing sense that these inquiring patients may be on to something, as international randomised controlled trials have now proven a survival benefit to adding radiotherapy (RT) to hormone therapy for men with locally advanced disease [1,2]. From early in 2013, the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial will investigate whether treatment directed against the primary tumour might indeed retard metastatic progression and thereby prolong survival by testing the role of RT-to-the-prostate in men presenting with metastatic disease.

Rationale

There are several lines of evidence to support the testing of prostate RT in men with metastatic disease.

1. The Primary Tumour May Prepare the 'Soil' for Metastasis

We now know that, far from being merely the source of the 'seed', the primary tumour also helps to prepare the 'soil'. Kaplan et al. [3] were the first to show that the initial event at a metastatic site is not the arrival of tumour cells, but rather the clustering of bone marrow-derived cells (BMDCs). These BMDCs make the local microenvironment of the secondary organ more receptive to tumour cell colonisation. It has since been found that recruitment of these BMDCs from the marrow is stimulated by endocrine factors released by the primary tumour [4]. An implication of this work is that therapy directed at the primary tumour, by abrogating this endocrine signalling, could retard the formation and the growth of distant metastases.

2. Cytoreductive Nephrectomy Provides Proof of Principle

Therapy directed against the primary tumour in the presence of metastatic disease has been evaluated rigorously in only one malignancy: RCC. Two cooperative groups ran randomised trials of radical nephrectomy in this setting [5,6]. The trials enrolled patients with previously untreated metastatic RCC whose primary tumours were amenable to surgical resection. Patients were randomised to receive the standard systemic therapy of the day, interferon α, either alone or with radical nephrectomy. Adding nephrectomy was shown to significantly improve median survival from 7 to 17 months in one trial [6], and

from 8 to 11 months in the other [5]. The mechanism by which nephrectomy improves survival remains uncertain, but is compatible with the theory that factors secreted by the primary tumour promote metastatic progression.

3. Supporting prostate cancer data

Weckermann et al. [7] collected bone marrow aspirates from a large cohort of patients with clinically localised prostate cancer treated by radical prostatectomy. Detection of disseminated tumour cells (DTCs) in bone marrow before prostatectomy conferred a five-fold increased risk of developing metastases. Conversely, DTCs detected after surgery were not associated with any excess risk. Thus, the risk of metastatic dissemination posed by DTCs was restricted to men with an intact primary tumour. This observation is consistent with the theory that factors derived from the primary tumour are required to stimulate DTCs to colonise and grow into overt metastases.

New STAMPEDE Research Arm: Prostate RT for Men with Metastatic Disease

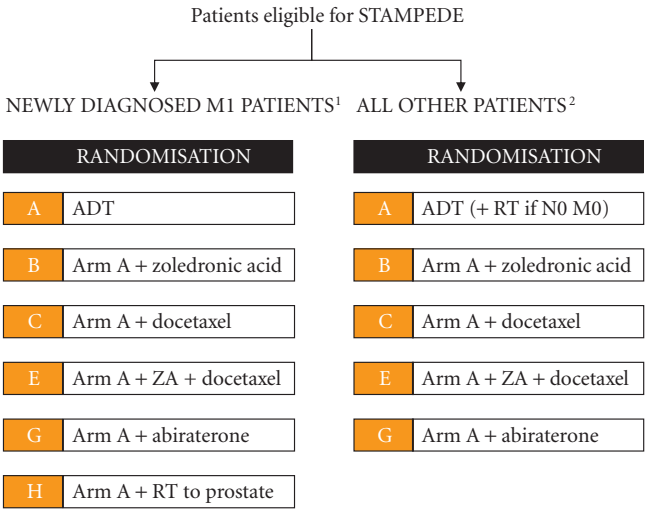
We hypothesise that local therapy to the primary site may retard distant disease progression and prolong survival in patients who first present with metastatic prostate cancer. This proposal will be tested in the STAMPEDE trial (registered as NCT00268476) by including a new comparison: prostate RT for patients with metastatic disease.

Design Considerations

Following the same processes used for the addition of an abiraterone comparison to STAMPEDE from November 2011 [8], a new research arm is being included in the trial's randomisation by protocol amendment. This new arm (which will be referred to as Arm H) will be hormone therapy plus RT to the prostate. The STAMPEDE trial recruits a broad spectrum of men, including high-risk non-metastatic patients and patients who have failed previous local therapy. These patients cannot, of course, be allocated to Arm H. Only patients with newly diagnosed metastatic disease and no contraindication to RT can be allocated to the new arm. As with all the existing arms, these patients will be compared only against the same subset of patients who are contemporaneously allocated to the control arm, hormone therapy alone (Arm A). Figure 1 depicts the flow of future patients joining the trial. Adding new questions by protocol amendment is both much quicker and much cheaper than setting up a new (and competing) trial and is hence an efficient use of scarce research resources.

A relative improvement of 25% in overall survival (hazard ratio 0.75) is the target, as for the other arms. There will be

Fig. 1 Future trial design of STAMPEDE. ADT, androgen-deprivation therapy; ZA, zoledronic acid.



[1]except pts with a contra-indication to RT

[2]all suitable pts with newly diagnosed locally advanced disease should also have RT[1]

an equal allocation ratio, and the same intermediate lack-of-sufficient-activity guidelines will be used as for the other on-going comparisons. Accounting for co-recruitment to the trial's other comparisons, ≈1200 metastatic patients will be included in this comparison, with 600 of them allocated to RT-to-the-prostate. Important secondary outcome measures will be RT toxicity and the complications of uncontrolled pelvic disease (such as the need for ureteric stents, TURP or colostomy).

RT Technique

The RT treatment aims to deliver a high dose for local tumour control using a simple technique in a convenient, patient-friendly schedule. The clinical target volume (CTV) will consist of the prostate gland alone, while the base of the seminal vesicles should also be included if they are involved by the primary tumour. The planning target volume (PTV) will have an 8-mm margin posteriorly, and a 10-mm margin in other directions around the CTV to account for prostate gland motion and uncertainty in daily treatment setup. These treatment volume definitions are recommended guidelines, but may be altered at the investigator's discretion in particular circumstances. For example, the posterior PTV margin may be adjusted according to the rectal diameter. Two dose-fractionation schedules are permitted according to patient and clinician choice: either 36 Gy in six fractions, administered weekly over 5 consecutive weeks, or 55 Gy in 20 fractions, administered daily, 5 days/week, over 4 weeks. RT will start promptly after randomisation, sooner than the standard-of-care RT used for M0 patients in the trial, who

have at least 6 months of hormone therapy before their RT. The rationale for this is that median time to progression in metastatic patients is relatively short and delayed RT could result in significant numbers of Arm H patients not receiving their allocated treatment before progression.

Timelines

Based on the current excellent rate of recruitment to STAMPEDE, we anticipate that accrual to the new arm should be complete ≤4 years of activation (i.e. RT for metastatic prostate cancer before the end of 2016) with overall survival data available around 2018. A positive result could spur on the evaluation of primary tumour-directed therapy in the face of metastatic disease in other cancers.

The STAMPEDE trial may now be effectively regarded as a programmatic collection of studies in advanced prostate cancer within one protocol rather than a single trial in the conventional sense. The STAMPEDE Trial Management Group is actively considering, and seeking suggestions for, further comparisons that could be addressed, either across the whole trial or in defined subsets as in this case. The original trial arms included three regimens (docetaxel, zoledronate and the two drugs combined) that have now successfully completed all interim analyses and will close to recruitment Spring 2013 with survival data expected in 2015. We are therefore also seeking suggestions for studies of relapsing patients, both for these arms and the more recent abiraterone arm. The first such trial with which the STAMPEDE Trial Management Group is engaging, CANTATA, will compare docetaxel re-challenge with cabazitaxel treatment in patients relapsing in the docetaxel arms. We welcome proposals from active researchers.

If you would like any further details about the STAMPEDE trial, please contact: stampede@ctu.mrc.ac.uk.

Acknowledgments and Conflicts of Interest

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References

1 **Warde P, Mason M, Ding K et al.** Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet* 2011; 378: 2104–11

2 **Widmark A, Klepp O, Solberg A et al.** Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009; 373: 301–8

3 **Kaplan RN, Riba RD, Zacharoulis S et al.** VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature* 2005; 438: 820–7

4 **Psaila B, Lyden D.** The metastatic niche: adapting the foreign soil. *Nat Rev Cancer* 2008; 9: 285–93

5 **Flanigan RC, Salmon SE, Blumenstein BA et al.** Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001; 345: 1655–9

6 **Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R.** Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001; 358: 966–70

7 **Weckermann D, Polzer B, Ragg T et al.** Perioperative activation of disseminated tumor cells in bone marrow of patients with prostate cancer. *J Clin Oncol* 2009; 27: 1549–56

8 **Sydes MR, James ND, Mason MD et al.** Flexible trial design in practice – dropping and adding arms in STAMPEDE: a multi-arm multi-stage randomised controlled trial. *Trials* 2011; 12 (Suppl. 1): A3

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Abbreviations: BMDC, bone marrow-derived cell; CTV, clinical target volume; DTC, disseminated tumour cell; PTV, planning target volume; RT, radiotherapy; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.