

TRAPEZE: a randomised controlled trial of the clinical effectiveness and cost-effectiveness of chemotherapy with zoledronic acid, strontium-89, or both, in men with bony metastatic castration-refractory prostate cancer

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Scientific summary

TRAPEZE: effectiveness of chemotherapy with ZA, Sr-89, or both

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Scientific summary

Prostate cancer is a major health problem worldwide and accounts for nearly one-fifth of all newly diagnosed male cancers. In the UK, approximately 35,000 men are diagnosed with prostate cancer each year, and in 2008 almost 10,000 men died from the disease. The disease is mostly one of older age, but significant numbers of men of working age will develop the disease.

Although prostate cancer most often presents as local disease, a significant proportion of patients progress despite initial treatment with ablative surgery or radiotherapy, often in combination with hormonal therapy. A minority of patients present with de novo metastatic disease.

Hormone therapy has been the mainstay of treatment for relapsed prostate cancer since the seminal studies of Huggins and Hodges, published in 1941, demonstrating substantial and prolonged remissions from prostate cancer with the use of either surgical castration or oestrogen therapy (Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941;**1**:293–7). Responses to hormone therapy typically last 18–24 months, depending on disease stage. This period after failure of initial androgen deprivation therapy was previously known as hormone-refractory prostate cancer. However, with the recognition that relapsing tumours remain dependent on androgen receptor-mediated pathways and the recent licensing in relapsing disease of abiraterone, a steroid synthesis inhibitor, and enzalutamide, an androgen receptor-targeting agent, the term castration-refractory prostate cancer (CRPC) is increasingly used and will be the preferred term in this report.

Chemotherapy with docetaxel is also a mainstay of therapy for metastatic castration-refractory prostate cancer (mCRPC) following two landmark trials published in the *New England Journal of Medicine* in 2004 (Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, *et al.* Docetaxel plus prednisolone or mitoxantrone plus prednisolone for advanced prostate cancer. *N Engl J Med* 2004;**351**:1502–12; and Petrylak DP, Tangen CM, Hussain MH, Lara PN, Jr., Jones JA, Taplin ME, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisolone for advanced refractory prostate cancer. *N Engl J Med* 2004;**351**:1513–20). Both trials showed improved palliative outcomes compared with mitoxantrone and, very importantly, an overall survival advantage for 3-weekly docetaxel and the docetaxel–estramustine combination with hazard ratios (HRs) of 0.76 and 0.8, respectively. On the basis of these trials, a 3-weekly schedule of docetaxel plus prednisolone for up to 10 cycles has emerged as the standard of care for mCRPC/CRPC and was approved by the National Institute for Health and Care Excellence (NICE) for this purpose in 2006. A number of post-chemotherapy treatments have been licensed on the basis of improvements in overall survival since 2010, including cabazitaxel, abiraterone and enzalutamide.

In patients with mCRPC, one of the most common sites of spread is bone, and bone metastases are a major cause of morbidity in men with CRPC. Bone morbidity is often quantified in clinical trials via a composite end point termed the skeletal-related events (SREs):

- pathological fracture
- spinal cord compression
- radiotherapy to bone
- hypercalcaemia
- change in anticancer treatment to treat bone pain.

Bisphosphonates inhibit bone catabolism by reducing the numbers of functioning osteoclasts and have been used to manage bone metastases. Zoledronic acid (ZA), but not some older bisphosphonates, also arrests cell proliferation, induces apoptosis and inhibits the growth factor stimulation of cultured prostate cancer cells. In trials in relapsing mCRPC, ZA reduced the time to SREs, as well as the frequency of subsequent SREs. The ZA licensing trials have proved very controversial, as the fracture end point was assessed by regular skeletal survey

with blinded radiological assessment. Hence, there is significant doubt as to whether many of the small fractures detected were precursors of a subsequent real 'clinical' SRE or radiological features of no significance. ZA is not currently recommended for use in the UK by NICE because of doubts as to its cost-effectiveness.

Radioisotopes have been used to palliate bone pain for over 20 years. A variety of radioisotopes are available; the most commonly used during the trial recruitment era were strontium-89 (Sr-89) and samarium-153. Both accumulate selectively in bone metastases compared with non-involved bone. There is some evidence that Sr-89 may reduce overall health-care costs compared with standard methods of delivering radiotherapy. There are a number of previous studies of combined use of chemotherapy with radioisotopes. Of particular note, Tu *et al.* combined combination chemotherapy with Sr-89 in a small randomised trial with promising results, suggesting a survival advantage in chemotherapy responders allocated to Sr-89 (Tu SM, Millikan RE, Mengistu B, Delpassand ES, Amato RJ, Pagliaro LC, *et al.* Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet* 2001;**357**:336–41).

This study sought to assess whether or not the addition of Sr-89 or ZA offers a significant benefit in combination with docetaxel and prednisolone in CRPC metastatic to bone. The primary research questions of the study are as follows:

- Does upfront use of bone-targeting agents with chemotherapy improve clinical outcomes?
- Is it more cost-effective to prevent bone complications or to treat them as they arise?

Design

This is a randomised controlled Phase III trial with a two-by-two factorial design which proceeded seamlessly from a randomised controlled four-arm Phase II trial. The Phase II trial objectives were to compare the four trial arms with respect to feasibility, tolerability and safety. The Phase III trial objectives were to assess treatments with respect to efficacy within a two-by-two factorial design framework; that is, the trial compared ZA with no ZA (stratified for Sr-89 use) and Sr-89 with no Sr-89 (stratified for ZA use). The primary outcome measures for the Phase III trial were both clinical progression-free survival (CPFS) (defined in relation to bone) and cost-effectiveness.

The Phase II end points of feasibility, tolerability and safety are subsumed within Phase III of the trial as secondary outcomes. The funding for Phase II was not provided by the Health Technology Assessment (HTA) programme of the National Institute for Health Research, and the preliminary Phase II analysis formed the basis of the HTA programme application for funding. We do not propose to present detailed analysis of the Phase II subset of patients in this report, as feasibility is confirmed by the successful completion of the Phase III trial.

Setting

UK oncology departments.

Participants

Men with CRPC metastatic to bone who are eligible for treatment with first-line chemotherapy.

Interventions

Arm A: docetaxel 75-mg/m² intravenously 3-weekly for up to 10 cycles.

Arm B: docetaxel as above plus ZA 4-mg intravenously 3-weekly during chemotherapy, then 4-weekly until disease progression.

Arm C: docetaxel as above for six cycles, Sr-89 150 MBq, then further docetaxel up to total of 10 cycles.

Arm D: docetaxel plus both Sr-89 and ZA as above.

Main outcome measures

Phase II

Primary: feasibility, tolerability and safety in terms of cycles of docetaxel and ZA and Sr-89, cycle delays, dose reductions and toxicity.

Secondary: CPFS, SRE-free survival, pain progression-free interval, overall survival (OS), costs, quality of life (QoL).

Phase III

Primary: CPFS, costs and cost-effectiveness.

Secondary: SRE-free survival, pain progression-free interval, OS.

All phases: additional substudies not part of this report

Changes in bone mineral density, biological profiling for prognostic and predictive indicators, prostate-specific antigen-related outcomes, patient-reported pain-related outcomes.

Data sources (if applicable)

Data were collected by research staff in the treating hospitals on standard case report forms.

Statistical methods

The trial examined the clinical efficacy of adding bone-targeting treatment to standard chemotherapy. Assuming that clinically worthwhile differences were seen, the costs associated with the extra therapy were analysed and used to estimate the clinical cost-effectiveness of the trial interventions. If no significant differences were seen, or if the trial interventions worsened outcomes, then the health economic analysis was clearly considered redundant.

The clinical analysis was conducted under a two-by-two factorial design; as such, we can consider the results of Sr-89 and ZA comparisons separately. In addition, in the interests of clarity, we shall also present the results of the health economic evaluation separately.

Clinical analysis

Strontium-89 comparison

In the control arm, median time to CPFS was 8.8 months from randomisation. This increased to 9.8 months with the addition of Sr-89 after cycle 6 [HR for benefit of 0.85 on multivariable analysis, 95% confidence interval (CI) 0.77 to 0.99; $p = 0.036$]. As some patients did not complete six cycles of chemotherapy, they did not get to the point of receiving Sr-89; we therefore did a second analysis restricted to those patients completing six cycles of chemotherapy. Resetting the time to progression from the sixth chemotherapy cycle makes the time to progression 4.3 months and 5.3 months, respectively, to give a HR for benefit of 0.8 on multivariable analysis (95% CI 0.66 to 0.97; $p = 0.024$). There was no improvement in overall survival (HR 0.97, 95% CI 0.82 to 1.15).

Zoledronic acid comparison

In the ZA arm, median control time to CPFS was, again, 8.8 months from randomisation. This also increased to 9.7 months, but the difference was not statistically significant (HR 0.94, 95% CI 0.81 to 1.10; $p = 0.457$). There was also no improvement in overall survival (HR 1.01, 95% CI 0.85 to 1.20). ZA did, however, show a highly significant effect on skeletal-related event-free interval (HR 0.76, 95% CI 0.63 to 0.93; $p = 0.008$). There was no improvement in overall survival (HR 1.01, 95% CI 0.85 to 1.20).

Economic evaluation

Strontium-89 comparison

The most prominent difference in mean patient costs between the Sr-89 and no Sr-89 groups is a result of the cost of the Sr-89 radioisotope itself. Apart from higher cost of Sr-89, the Sr-89 group was associated with a greater cost for docetaxel and ZA given as protocol treatments, higher cost of cabazitaxel and docetaxel provided as concomitant medications and increased cost because of surgery. On the other hand, this group was associated with a lower use of radiotherapies, abiraterone, ZA and Sr-89 as concomitant medications, as well as fewer inpatient days, outpatient appointments and GP visits. This resulted in a mean cost difference of £1341 (95% bias-corrected and accelerated bootstrap method 95% CI –£66 to £2748). In terms of quality-adjusted life-years (QALYs), patients receiving Sr-89 presented a slightly greater number (0.08) of QALYs than those not receiving Sr-89. The point estimate incremental cost-effectiveness ratio (ICER) for Sr-89 compared with that for no Sr-89 was calculated at £16,590 per additional QALY. For prices of an administration of Sr-89 up to £2120, the ICER for Sr-89 remains below the £20,000 per QALY mark.

Zoledronic acid comparison

The difference in mean patient costs between the ZA and no ZA groups was, to a great extent, because of the use of ZA (mean difference £2197). Excluding the use of ZA, patients in the ZA group presented lower resource use and costs than those in the no ZA group. In particular, there were significant differences in the use of radiotherapy and surgery for skeletal-related problems. If ZA is considered as a branded product with an acquisition cost of £174 for a 4-mg dose, the difference in total cost between ZA and no ZA is £1319. On the other hand, taking into account the availability of generic ZA at a significantly lower cost reduced the difference in total cost to £251. In terms of QALYs, ZA appeared to be slightly more effective than no ZA, resulting in a gain of 0.03 QALYs. The additional costs and the small but positive change in QALYs in favour of ZA resulted in ICERs of £8005 for the generic-based price and £42,047 for the proprietary product. Whether or not the addition of ZA to chemotherapy represents a cost-effective use of resources depends largely on the acquisition cost of a 4-mg dose of ZA. If this acquisition cost is up to £98, which is the most likely scenario because of the availability of generic ZA, the ICER for ZA is below £20,000 per QALY and, thus, this option is cost-effective at this ceiling ratio.

Conclusions

In terms of impact on the primary outcome measure of bony progression-free survival, the Sr-89 arm was positive but with a relatively modest absolute benefit and no improvement in OS. In contrast, there was no evidence that the ZA arm was of benefit for the primary outcome measure and OS, but there was evidence of a benefit in terms of impact on SRE-free interval and total SRE numbers. On the basis of the positive effects seen, undertaking the health economic evaluation for both agents was considered worthwhile.

The impact of the trial therapies on the primary outcome measure of cost-effectiveness is interesting. Although associated with relatively modest benefits, Sr-89 met the cost-to-QALY ratio of less than £20,000 that is considered to represent effective use of NHS resources. In contrast, ZA had more tangible clinical benefits in the form of a substantial reduction in SREs and increased time to first SRE. These did not translate into sizeable QoL benefits, as QoL was maintained by increased use of other therapies, particularly surgery and radiotherapy. Hence, patients traded attendance for a predictable preventative therapy for attendances for needs-driven palliative therapies. The ICER for proprietary ZA is high, at £42,047, largely because of the lack of impact on QoL. As noted above, taking into account the recent availability of generic ZA at low prices, ZA resulted in an additional cost of £251 and an ICER of £8005. Given the pressure on NHS emergency resources, trusts may consider this cost to be good value for money, as it converts unpredictable events such as fracture or spinal cord compression into predictable outpatient workload. Additional analyses on the basis of data from the Hospital Episode Statistics data set would allow corroborating the findings of this study. Further research into the use of ZA (and other bone-targeting therapies) with newer prostate cancer therapies would be desirable.

Study registration

This trial is registered as ISRCTN12808747.

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For more information about the HTA programme please visit the website: <http://www.nets.nihr.ac.uk/programmes/hta>

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