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RESEARCH HIGHLIGHT

COX-2 inhibitors in prostate cancer treatment—hold your horses?

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Cyclo-oxygenase has been implicated as a potential therapeutic target in prostate cancer. However, the ongoing multi-arm randomized controlled STAMPEDE trial has failed to show a benefit of the cyclo-oxygenase 2 inhibitor celecoxib in men with locally advanced or metastatic prostate cancer also receiving androgen deprivation therapy. STAMPEDE uses a novel adaptive design that allows testing of different therapeutic interventions, and should generate much needed novel information regarding evidence-based prostate cancer management.

The first results from the ongoing STAMPEDE trial just reported online in *The Lancet Oncology* by Nicholas James and colleagues have shown no advantage of adding celecoxib to standard hormone therapy for men with prostate cancer.[1] This large multi-arm multistage multicenter open-label randomized controlled trial uses a novel adaptive design to simultaneously determine the efficacy of various systemic therapies in men already receiving androgen deprivation therapy (ADT) for prostate cancer.[2] While the definitive primary outcome of STAMPEDE is overall survival, it uses failure-free survival (FFS) as the intermediate outcome to adaptively focus accrual away from less encouraging research arms, in turn increasing the recruitment into the more promising treatment arms.

In STAMPEDE, 2043 men with high-risk locally advanced or metastatic prostate cancer receiving first-line long-term ADT (98% were given luteinizing hormone releasing hormone analogues) were randomized to one control arm (ADT alone) and five trial arms to assess whether concomitant use of ADT plus the addition of one or two drugs (docetaxel, zoledronic acid, celecoxib, zoledronic acid and docetaxel, or zoledronic acid and celecoxib) improves survival.

The current publication from STAMPEDE reports on the effects of celecoxib, added to ADT, on FFS defined as the first of: prostate-specific antigen (PSA) failure (>4 ng ml^{-1} and $>50\%$ above nadir); local progression; nodal progression; progression of existing metastases or development of new metastases; or death from prostate cancer. The rationale for testing the hypothesis that celecoxib, a cyclo-oxygenase-2 (COX-2) inhibitor has therapeutic efficacy in prostate cancer was based on observational evidence associating the use of non-steroidal anti-inflammatory drugs with reduced risk of prostate cancer.[3,4] Furthermore, COX-2 expression has been reported to be upregulated in carcinomas[5] including prostate cancer[6] and celecoxib may induce apoptosis in prostate cancer cells.[7]

In STAMPEDE, 584 patients were allocated to receive ADT alone, and 291 men received celecoxib at a dose of 400 mg twice daily, given up to one year in light of possible adverse cardiovascular effects,[8] in addition to ADT. The minimum pre-specified target for allowing ongoing recruitment into the COX-2 treatment arm was a 9% absolute improvement of FFS, corresponding to hazard ratio of 0.92.

At the preplanned analysis, 209 FFS event had occurred in the ADT-only arm, and 96 in the ADT plus celecoxib arm, corresponding to a hazard ration of 0.98 (95% CI: 0.90–1.06). Two-year FFS was 51% (95% CI: 46–56) in the ADT-only arm and 51% (95% CI: 43–58) in the ADT plus celecoxib arm. PSA failure was the most common cause of FFS, accounting for 78% of FFS events in both groups. Given the failure to reach the pre-specified target for benefit, the independent data monitoring board recommended stopping recruitment into the celecoxib arm, and this was endorsed by the trial steering committee.

There was no difference in the incidence of adverse event between groups, with grade 3–5 toxicities reported in 23% (95% CI: 20–27) in the ADT arm and 25% (95% CI: 19–30) in the ADT plus celecoxib arm, the commonest being endocrine effects related to ADT. There was no difference in cardiovascular events, although numbers were few and the study was not powered for this outcome.

Before turning all horses away from COX-2, is there still more to the COX-2 inhibition story? STAMPEDE uses FFS as an important outcome on the causal pathway to overall survival, based on the assumption that a treatment that improves overall survival will first show an improvement in FFS. This assumption, however, may not be true and has not been valid in some other prostate cancer studies. The immunotherapy agent sipuleucel-T showed no benefit in PSA progression, but did show an overall benefit in survival.[9] As noted by the authors, celecoxib's actions may not be reflected in PSA-based measures of FFS and as such forthcoming longer-term overall survival results are awaited.

There are several possibilities as to why COX-2 inhibition has not shown evidence of efficacy. Firstly, new evidence has emerged, available after STAMPEDE was designed, which has cast doubt on COX-2 as a therapeutic target in prostate cancer. In a short-term (4–6 weeks) randomized controlled trial of neoadjuvant celecoxib prior to prostatectomy in men with localized prostate cancer, histopathological examination of operative specimens showed that COX-2 expression was significantly lower in malignant prostate cells than benign cells.[10] In addition, celecoxib had no effect on biomarkers of prostate carcinogenesis, despite adequate tissue penetration. In addition, the COX-2 inhibitor rofecoxib had no effect on overall survival

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or recurrence in a large randomized controlled trial of 2434 patients with colorectal cancer.[11]

Secondly, given that patients in STAMPEDE were not tested for COX-2 expression in their tumours, it remains possible that a subgroup of patients who overexpress COX-2 in their prostate cancer cells may have specific benefit from celecoxib. This hypothesis would need to be tested in future COX-2 inhibitor trials in patients stratified according to tumour COX-2 expression status.

Thirdly, limiting celecoxib treatment to one year, although understandable in the light of the fact that patients receiving ADT are already at high cardiovascular risk,[12] may have been too short to show evidence of activity. Two recent meta-analyses suggest that daily aspirin, a non-selective cyclo-oxygenase inhibitor, is effective in preventing adenocarcinoma incidence (including prostate), the development of distant metastases and cancer-related deaths; however, this effect is mainly seen after 5 years of treatment.[13,14]

These first results provide a window into the possibilities from the STAMPEDE study. Above caveats aside, the current evidence suggests that celecoxib has limited therapeutic utility in prostate cancer. Unless new clinical data supporting their use become available, the use of COX-2 inhibitor therapy for treatment of high-risk prostate cancer cannot be recommended.

The other therapy arms of STAMPEDE are galloping ahead, and its novel adaptive design allows for testing of new therapeutic regimens. Indeed, a recent abiraterone trial arm has been added in November 2011, and the use of radiotherapy in newly diagnosed locally advanced N0M0 disease has been mandated when the results showing a survival benefit of radical radiotherapy for such patients became available.[15] Other emerging new prostate cancer therapies may well become future STAMPEDE trial arms. Therefore, we look forward to future outcomes of the STAMPEDE trial in the hope that its results will allow us to select the most promising therapeutic horses in the race against prostate cancer.

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