Radiotherapy for newly diagnosed oligometastatic prostate cancer

Amelie-Benoist/BSIP/Science Photo Library

Published Online
October 21, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32598-4

See Articles page 2353

The standard of care for metastatic prostate cancer is systemic therapy in the form of androgen deprivation therapy with or without novel antiandrogens or chemotherapy.[1] Administering local treatment to the primary tumour in the setting of metastatic prostate cancer has long been postulated to have a survival benefit on the basis of retrospective series.[2–7] But such series can have selection bias in that patients undergoing local treatment can also have a low volume of metastatic disease (oligometastases), creating a major confounder in most analyses. To date randomised controlled trials investigating this subject have been sparse, and the value of local control in metastatic prostate cancer has been debated.

In *The Lancet*, Christopher Parker and colleagues[8] present results of the STAMPEDE randomised controlled trial comparing standard of care (androgen deprivation therapy with or without docetaxel) with external-beam radiotherapy to the prostate. 2061 men with newly diagnosed metastatic prostate cancer who had received no previous treatment to the primary tumour were enrolled from 117 hospitals in Switzerland and the UK. Radiotherapy improved failure-free survival compared with standard of care alone (hazard ratio [HR] 0·76, 95% CI 0·68–0·84; p<0·0001), but overall survival was not improved (0·92, 0·80–1·06; p=0·266). However, in a prespecified analysis, men were stratified using the CHAARTED[9] definition for low or high metastatic burden. In patients with a low metastatic burden (n=819), radiotherapy improved 3-year overall survival compared with standard of care (81% *vs* 73%; HR 0·68, 95% CI 0·52–0·90; p=0·007), and failure free survival was also improved (0·59, 0·49–0·72; p<0·0001). Patients with a high metastatic burden did not benefit from radiotherapy in terms of failure-free survival or overall survival. Parker and colleagues concluded that radiotherapy should be an option for men with newly diagnosed metastatic prostate cancer and a low metastatic burden.[8]

A relevant trial in this area of research is the HORRAD study.[10] 432 men with metastatic prostate cancer were randomly allocated androgen deprivation therapy either alone or with radiotherapy. No difference in overall survival was noted between the two treatment groups, but in the subgroup of men with low volume of metastatic disease (n=160), radiotherapy showed some improvement in overall survival (HR 0·68, 95% CI 0·42–1·10), although the finding was not significant. The similar effect size for radiotherapy in men with low metastatic burden in the HORRAD and STAMPEDE trials, but the absence of statistical significance in HORRAD, suggests that HORRAD was underpowered from the standpoint of metastatic burden. We estimate that more than 250 men would have needed to be randomised to have an 80% probability of detecting a difference with an HR of 0·75. Taken together, both these trials build the case for local radiotherapy in selected men with newly diagnosed oligometastatic prostate cancer.

As with any trial, STAMPEDE does have several limitations. First, the main finding of improved survival with radiotherapy in the cohort with a low metastatic burden is based on a subgroup analysis and should be interpreted cautiously. Next, the analysis did not test various definitions of oligometastatic prostate cancer, leaving open the possibility for patients with (for instance) five bone metastases to potentially benefit from local therapy. Defining a metastatic volume threshold above which patients are unlikely to benefit from local therapy is an important area of further study. Also, metastatic deposits in STAMPEDE were identified using conventional imaging, and such a trial might hold less weight as more sensitive PET imaging becomes commonplace. The trial also did not comment on patients with non-regional (eg, retroperitoneal or thoracic or other) lymph-node-only metastases, a relatively common scenario. Do they benefit more from cytoreductive radiotherapy than the average oligometastatic patient with bone metastases? Moreover, the incidence of symptomatic local events was similar between control and radiotherapy groups, suggesting that radiotherapy might not add much local control benefit beyond androgen deprivation therapy with the dosage used in STAMPEDE—a counterintuitive finding. Furthermore, the total dose of radiation delivered in STAMPEDE (either 36 Gy in six fractions or 55 Gy in 20 fractions) was significantly lower than the

70 Gy or greater given for high-risk localised prostate cancer.[11] Thus, dose-optimisation studies are needed to reach a balance between local and oncological control and quality of life in the metastatic setting.

Based on the findings of STAMPEDE,[8] radiotherapy could be considered for patients with newly diagnosed oligometastatic prostate cancer, but further studies are needed to delineate the clinical implementation of such treatment.

*Luca Boeri, Vidit Sharma, *R Jeffrey Karnes*
Department of Urology, Mayo Clinic, Rochester, MN 55905 USA (LB, VS, RJK); and Department of Urology, IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy (LB)
karnes.r@mayo.edu

We declare no competing interests.

1 Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer, part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol* 2017; **71:** 630–42.
2 Bayne CE, Williams SB, Cooperberg MR, et al. Treatment of the primary tumor in metastatic prostate cancer: current concepts and future perspectives. *Eur Urol* 2016; **69:** 775–87.
3 Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. *Eur Urol* 2014; **65:** 1058–66.
4 Löppenberg B, Dalela D, Karabon P, et al. The impact of local treatment on overall survival in patients with metastatic prostate cancer on diagnosis: a national cancer data base analysis. *Eur Urol* 2017; **72:** 14–19.
5 Leyh-Bannurah S-R, Gazdovich S, Budäus L, et al. Local therapy improves survival in metastatic prostate cancer. *Eur Urol* 2017; **72:** 118–24.
6 Rusthoven CG, Jones BL, Flaig TW, et al. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. *J Clin Oncol* 2016; **34:** 2835–42.
7 Pompe RS, Tilki D, Preisser F, et al. Survival benefit of local versus no local treatment for metastatic prostate cancer: impact of baseline PSA and metastatic substages. *Prostate* 2018; **78:** 1–5.
8 Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018; published online Oct 21. http://dx.doi.org/10.1016/S0140-6736(18)32486-3.
9 Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015; **373:** 737–46.
10 Boevé LMS, Hulshof MCCM, Vis AN, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. *Eur Urol* 2018; published online Sept 25. DOI:10.1016/j.eururo.2018.09.008.
11 Carroll PH, Mohler JL. NCCN guidelines updates: prostate cancer and prostate cancer early detection. *J Natl Compr Canc Netw* 2018; **16:** 620–23.

The extending scope of kinase inhibition in immune diseases

Published Online
October 22, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32600-X

See Articles pages 2367 and 2378

Functional mutation analyses in patients with immune deficiencies identified Janus kinases (JAKs) as plausible regulators of the immune response. Thereafter, elegant signalling biology generated a compelling rationale for the use of small molecule inhibitors to recapitulate the cytokine blocking activities of biologics. JAK inhibitors have thus emerged as novel immune modifiers that target cytokines via blockade of intracellular cytokine receptor signalling pathways. Four members of the family (JAK1, JAK2, JAK3, and TYK2) can form a variety of heterodimers (eg, JAK1/JAK2 and JAK1/JAK3) and transmit signals from the cell membrane to the nucleus (via cytosolic shuttling proteins) to activate leucocytes and stromal cells and drive inflammation.[1] In the past 5 years, JAK inhibitors were developed for the treatment of rheumatoid arthritis;[1] now attention has turned to their wider use across immune-mediated inflammatory diseases.

Spondyloarthritis comprises a group of clinically and pathogenetically related immune-mediated inflammatory diseases, including psoriatic arthritis and axial spondyloarthritis. These conditions impair quality of life and, by virtue of accelerated comorbidity, reduce life expectancy.[2,3] Although novel biological therapies, including inhibitors of tumour necrosis factor (TNF), interleukin (IL)-12/IL-23 p40, IL-17A, and IL-23 p19, have transformed the management of psoriatic arthritis,[2,4,5] and TNF and IL-17A inhibitors the management of axial spondyloarthritis,[6] unmet need remains for these lifelong, incurable conditions. Patients with psoriatic arthritis with articular and entheseal disease often only partly respond or do not respond at all to treatment, with few patients reaching sustained minimal disease activity. Moreover, pain control is suboptimal, and therapeutic tapering and drug-free remission remain challenging and rarely achieved goals. Orally bioavailable therapeutics are intriguing in this context. A phosphodiesterase type 4 inhibitor, apremilast, is approved for use in patients with psoriatic arthritis. More recently, tofacitinib (an inhibitor of JAK1/JAK3) showed efficacy in patients with psoriatic arthritis and ankylosing spondylitis, offering the first clue that JAK family inhibition might offer general benefits to patients with spondyloarthritis.[7,8]