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Clinical Studies Update

Local Treatment (Primary Tumor and Metastases) in Metastatic Prostate Cancer

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1. Introduction

The past decade has seen a notable improvement in the overall survival (OS) rate for patients with metastatic hormone-sensitive prostate cancer (mHSPC). This has been achieved by combining androgen deprivation therapy (ADT) with either docetaxel or an androgen receptor pathway inhibitor (ARPI) alone or as part of triplet therapy [1–4]. The concurrent HORRAD and STAMPEDE trials investigated the potential role of prostate radiotherapy (RT) in a population of patients with synchronous mHSPC receiving ADT alone as the standard of care (SOC). The STOPCAP meta-analysis of individual patient data from these two trials demonstrated a 7% absolute improvement in 3-yr OS for men with low-volume mHSPC who were predominantly treated with SOC and had fewer than five skeletal metastases [5]. The PEACE-1 trial assessed the efficacy of prostate RT in men with de novo low-volume mHSPC receiving intensified systemic treatments as a second preplanned primary endpoint [6]. Results demonstrated that prostate RT did not improve OS for men with de novo mHSPC and a low metastatic burden. Nevertheless, improvements in radiological progression-free survival (PFS) and time to castration resistance were observed for men receiving SOC + abiraterone acetate + RT. Interestingly, there was also a reduction in the incidence of severe urinary symptoms irrespective of metastatic burden in the RT arm.

Despite the absence of level 1 evidence, metastases-directed therapy (MDT) is an approach commonly used in the management of low-volume mHSPC. This is supported by two randomized phase 2 trials [7,8] in which MDT significantly increased PFS.

In this update, we describe results from a network meta-analysis by Roy et al [9] on the role of prostate RT in the treatment of low-volume mHSPC. We also discuss the long-term analysis of the STOMP and ORIOLE trials by Deek et al [10] regarding low-volume mHSPC with prior definitive treatment of the primary tumor.

2. Prostate RT in low-volume mHSPC

Roy et al [9] conducted a literature review and a network meta-analysis of RT in the subgroup with low-volume mHSPC within relevant trials. The treatment arms were grouped into four categories: SOC, SOC + ARPI, SOC + RT, and SOC + ARPI + RT. The main outcome measure was OS. The treatments were then ranked according to the surface under the cumulative ranking curve (SUCRA). A SUCRA value of 1 indicates that the treatment is the optimal choice, while a value of 0 indicates that it is the least preferred. A total of 4423 patients with mHSPC from ten randomized controlled trials were included in the analysis. The SOC + ARPI + RT combination resulted in a 47% reduction in the risk of death (pooled hazard ratio [HR] 0.53, 95% credible interval 0.34–0.81). The SUCRA values were 0.0006 for SOC, 0.45 for SOC + RT, 0.62 for SOC + ARPI, and 0.94 for SOC + ARPI + RT. Addition of RT to a combination of ARPI

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+ ADT (with or without docetaxel), corresponding to the contemporary SOC, resulted in a significant OS improvement in comparison to ADT in low-volume mHSPC. Further research is required to confirm these findings, including a meta-analysis with individual patient data from randomized clinical trials.

3. MDT in oligometastatic PC: long-term outcomes and analysis of the STOMP and ORIOLE trials

Initial reports from the STOMP and ORIOLE trials indicated that MDT in comparison to observation prolongs both ADT-free survival and PFS in low-volume mHSPC with prior definitive treatment of the primary tumor. Both were randomized phase 2 trials that enrolled patients with three or fewer metastases, identified via conventional imaging in ORIOLE and via choline positron emission tomography in STOMP, with random assignment to observation or MDT. Active systemic therapies were not allowed in combination with MDT. The primary end point was PFS. Time-to-event analysis was performed to detect differences in outcomes of interest using the Kaplan-Meier method, stratified by treatment (MDT vs observation) or high-risk mutational status. A long-term analysis of outcomes in these two trials included a total of 116 patients. The PFS for the pooled cohort was 11.9 mo in the MDT arm (95% confidence interval [CI] 8.0–18.3) versus 5.9 mo (95% CI 3.2–7.1) in the observation arm. This was reflected in a pooled HR of 0.44 (95% CI 0.29–0.66; $p = 0.001$). A total of 103 patients (89%) had tissue available for sequencing, and somatic next-generation sequencing was successful for 70 patients (60%). Patients with and without a high-risk mutation benefited from MDT. However, the potential for a benefit of greater magnitude was observed for those with a high-risk mutation. For tumors with a high-risk mutation, median PFS was 7.5 mo (95% CI 5.9–not reached [NR]) in the MDT arm versus 2.8 mo (95% CI 2–NR) in the observation arm (HR 0.05, 95% CI 0.01–0.28; $p < 0.01$). Long-term follow-up revealed that MDT continued to be associated with an increase in PFS. The encouraging PFS results suggest that in appropriately selected patients, SOC ± MDT might be a reasonable upfront option. However, results from ongoing randomized phase 3 trials are awaited to confirm the benefit of MDT for strong oncological outcomes and to identify patients who can benefit for this intensified strategy using relevant biomarkers [11].

Conflicts of interest: The authors have nothing to disclose.

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