Editorial Commentary

Identifying the relevant population for neoadjuvant chemo-hormonal therapy combined with radical prostatectomy

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High-risk localized PCa account for about 15% of cases at diagnosis (1) and it is particularly important to establish an appropriate treatment strategy for these patients, considering a multimodal approach and including both local and systemic therapies. Radical prostatectomy (RP) may be an option for selected patients with high-risk localized prostate cancer with an acceptable cancer-specific mortality (10–15%) at 10 years; however, oncological outcomes are decreasing for the subgroups of highest risk patients who have ≥ pT3 disease, Gleason score ≥8, and lymph node invasion. For these patients, the risk of recurrence is up to 70% at 10 years after RP (2).

We have read with interest the publication of Pan *et al.* entitled "Neoadjuvant chemohormonal therapy combined with RP and extended PLND for very high risk locally advanced prostate cancer: a retrospective comparative study" (3). In this article, the authors have clearly addressed the problem of identifying the relevant patient population. Indeed, there is probably a very high-risk population that really benefits from perioperative strategies. This multimodal approach probably offers the greatest chance of cure for men who may harbor occult metastatic disease.

The rationale for neoadjuvant systemic therapy is to reduce tumor volume, facilitating a complete surgical resection and reducing the risk of positive margins. It can also provide early systemic control of microscopic metastatic disease, thereby delaying time to progression and/or recurrence.

Data remains controversial regarding whether a neoadjuvant strategy may or may not benefit these patients with high-risk localized prostate. Data from phase 2 clinical trials of neoadjuvant chemotherapy without androgen deprivation therapy (ADT) showed no improvement in clinical outcomes (4-7). On the other hand, there is no evidence for a benefit of neoadjuvant ADT alone prior RP [biochemical progression-free survival (bPFS) and overall survival (OS)] although there is a tendency toward improved pathological results (particularly positive margins) compared to RP alone (8).

Thus, combined strategy with docetaxel-based chemo-hormonal therapy may have a role in eliminating pre-existing ADT-resistant tumor cells in the neoadjuvant setting. This chemo-hormonal strategy has already been tested before RP and has shown low rates of pathological complete response (less than 10% in most studies) (9-11). Recently, the prospective randomized phase III trial, Cancer and Leukemia Group B (CALGB) 90203 evaluated the benefit of neoadjuvant chemo-hormonal treatment in men with high-risk clinically localized prostate cancer and showed that neoadjuvant ADT plus docetaxel followed by RP did not increase 3-year bPFS compared with RP alone (12). However, given that a substantial portion of the patients in this study received additional treatment in a non-randomized fashion outside of the clinical trial, it is unknown what effect, if any, this may have had on OS.

Compared to CALGB 90203, the chemo-hormonal treatment arm in the current study had a more advanced clinical stage (98.3% of T3-T4 tumors and 55% of positive

lymph node disease). Indeed, the authors address the issue of very high-risk patients defined as a clinical stage more than cT3a, or primary Gleason pattern 5 or ≥5 cores with Gleason sum 8 to 10, or PSA ≥50 ng/mL, or with pelvic metastatic lymph node involvement. It should be noted that only 48% of patients had an undetectable postoperative PSA, and 81% of patients with undetectable PSA experienced early biochemical recurrence (median time of 9 months) if RP alone, thus justifying salvage therapy. This subpopulation therefore has a particularly poor prognosis and a neoadjuvant chemo-hormonal combination is more likely to have a benefit in this context. Although the follow-up is still insufficient, especially for the chemo-hormonal treatment arm, and despite the retrospective design of the study, the oncological outcomes are interesting in terms of bPFS. OS data will incorporate the impact of any adjuvant or salvage postoperative therapy.

Beside neoadjuvant strategy, several trials have assessed the chemo-hormonal strategy in an adjuvant setting after RP and showed no improvement in OS (13). Nevertheless, these studies included heterogeneous patient populations.

Finally, while the authors probably identify the most relevant population justifying a neoadjuvant or adjuvant chemo-hormonal strategy, the question of optimal local treatment remains. A very high-risk localized prostate cancer may probably be discussed for radiation therapy in combination with hormonal treatment, especially if PSA >50 ng/mL or lymph node involvement. A meta-analysis of 11 trials evaluating docetaxel in men with non-metastatic prostate cancer, including GETUG-12, RTOG 0521, and STAMPEDE, showed no benefit in OS with the addition of docetaxel to radiotherapy in combination with hormonal treatment (14). Several trials are still ongoing to assess the benefit of chemotherapy in association with radiotherapy and hormonal treatment, such as the phase III PEACE 2 (GETU-AFU 23) trial that evaluates four cycles of neoadjuvant cabazitaxel and/or pelvic radiotherapy in combination with ADT and prostate radiotherapy.

Neoadjuvant or adjuvant strategies also call into question about the efficacy of subsequent therapies in case of metastatic progression. In the ancillary study of CALGB 90203, it is remarkable that there is a heterogeneity of treatment response with some upregulation of AR-V7 expression as well as a subset of neuroendocrine and plasticity genes, which could probably serve as potential early molecular markers of resistance (15).

The two challenges of the next few years will be to integrate next-generation hormone therapy into this neoadjuvant/adjuvant setting and to identify patients who could really benefit from such a strategy by avoiding unnecessary toxicities.

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Footnote

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