Editorial Commentary

The docetaxel debate: impact of chemotherapy in high-risk non-metastatic prostate cancer

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Taxanes have an established role in the management of metastatic prostate cancer (1-5) but much controversy still exists in their application for men with high risk non-metastatic disease. Much of this controversy is due to the varied settings in which they have been studied as for instance primary treatment with radiation and androgen deprivation therapy *vs.* post-prostatectomy and by wide ranging risk factors such as node positive disease, Gleason score, elevated PSA, or T3/T4 disease.

Oudard *et al.* in the publication of their phase III trial "Effect of Adding Docetaxel to Androgen-Deprivation Therapy in Patients With High-Risk Prostate Cancer With Rising Prostate-Specific Antigen Levels After Primary Local Therapy: A Randomized Clinical Trial" as reported in *JAMA Oncology* have added both to our understanding and the controversies surrounding the use of docetaxel in the treatment of non-metastatic prostate cancer (6). The objective of the study was to assess the benefit of ADT plus docetaxel in patients with rising PSA after primary local therapy and high risk factors but no evidence of metastasis. The primary hypothesis was that 3-year PSA-PFS rate in the docetaxel arm would be superior to that in the ADT arm by 15% (81% *vs.* 66%). This hypothesized improvement corresponded with median PFS times of 9.8 *vs.* 5.0 months as calculated using an exponential event distribution. High-risk factors were defined as N1 disease, positive surgical margins, Gleason score ≥8, PSA velocity greater than 0.75 ng/mL per year, PSA doubling time ≤6 months and/or time to PSA recurrence of ≤12 months. Given the range of patients inclusive of prior surgery or radiation alone or surgery followed by salvage radiation, PFS progression was defined as a 50% or more relative increase above nadir accompanied by an absolute PSA increase defined in a sensitivity analysis with increase varied from 0.2 to 2.0 ng/mL confirmed by two additional PSAs.

A total of 254 patients were randomized between June 2003 and September 2007. Data analysis cutoff level for PSA-PFS was in January 2011 providing a median follow-up of 30 months. Median PSA-PFS was 20.3 months in the ADT + docetaxel arm *vs.* 19.3 months in the ADT alone arm (P=0.21). While there was no further analysis of the primary endpoint of PSA-PFS reported beyond 30 months, both radiographic PFS and overall survival were reported with follow-up extending out to 10.5 years with no differences noted. Quality of life also was not significantly different in the long-term.

The rates of PSA-PFS failure were notable in this study taking into account the 30-month median follow-up coupled with the use of 12 months of ADT followed by testosterone recovery and the requirement for 3 rising PSAs to confirm failure. Careful assessment of figure 2A in the paper showing longitudinal PSA-PFS reveals, as expected, few failures in the first 12 months during which time subjects were receiving ADT. Subsequently we see the

anticipated but here delayed exponential failure occur at a similar rate for both treatment groups with ultimate PSA-PFS rates approximating 25% at 30–36 months as compared to the stated estimates of 81% *vs.* 66% in the statistical design. The impact of this large discrepancy between the estimated and actual findings on the statistical assumptions is not discussed in the paper.

Ultimately however it appears at least in this trial that docetaxel did not have a significant impact on treatment outcomes in the setting of rising PSA after primary treatment. Of note, the authors report that a planned sensitivity analysis was performed in which the absolute PSA increase-defining progression varied from 0.2 to 2.0 ng/mL in 0.1 ng/mL increments never reached a HR of significance and therefore 0.2 ng/mL rise was chosen to define PSA progression. While there were diverse criteria used to define high risk patients, on sub-group analysis there were no significant differences favoring either treatment group. Clearly the largely overlapping curves showing lack of difference for PSA-PFS, radiographic PFS and overall survival are disappointing.

So how does this study compare and add to other studies assessing the use of docetaxel in high risk but non-metastatic prostate cancer?

Review of the literature provides insight into the role of docetaxel in a wide range of non-metastatic treatment settings. Specifically three other completed phase 3 randomized studies have addressed the impact of docetaxel in non-metastatic high-risk prostate cancer including primary use of radiation as local treatment in three and radical prostatectomy in the other (5,7,8). A 5th randomized trial, NRG GU002 is currently open to accrual also addressing the question of use of docetaxel in the post-prostatectomy setting (9). An important distinction of these trials with the exception of NRG GU002 is the focus on primary treatment as opposed to addition of docetaxel following initial local treatment failure as assessed by Oudard *et al.*

The STAMPEDE trial included nearly 40% of subjects who had either high-risk locally advanced non-metastatic prostate cancer defined as node-negative, with at least two of the following criteria: T3 or T4, Gleason ≥8 or PSA ≥40 ng/mL (24%) or node positive disease (15%). Subjects were randomized to at least 3 years of ADT with loco-regional radiation initially recommended and subsequently required for patients with node-negative disease and optional for patients with node-positive disease, or ADT with six cycles of docetaxel, 2 years of zoledronic acid, or both docetaxel and zoledronic acid. A total of 2,962 subjects were accrued. In subjects with non-metastatic disease, 62% received radiation, more so in the setting of N0 *vs.* N+ disease. The study revealed an overall survival benefit with addition of docetaxel. The biggest difference in survival was noted in metastatic patients, however, high-risk M0 patients also benefited from addition of docetaxel with a significant failure-free survival benefit of 9 months as compared with patients not receiving docetaxel with HR of 0.60. There was no benefit in overall survival noted in non-metastatic subjects with addition of docetaxel noting relatively few events in this more favorable subset of patients on the STAMPEDE trial (5).

GETUG 12 included patients with previously untreated prostate cancer and at least one high risk factor: T3–T4 disease, Gleason score of ≥8, PSA >20 ng/mL, or pathological node-positive disease. Subjects were randomized to receive either 3 years of goserelin along with four cycles of docetaxel and estramustine, or goserelin alone. Local therapy consisted of either radiation or prostatectomy in N0 patients or radiation or no local treatment in N1 patients noting all patients underwent lymph node dissection. 413 subjects were enrolled. Local treatment consisted of radiotherapy for 87% of patients. There was improvement in relapse-free survival with the addition of chemotherapy: 62% in the ADT plus docetaxel and estramustine arm *vs.* 50% in the ADT alone arm remaining relapse free at eight years. Relapse or death occurred in 43% in the ADT plus docetaxel and estramustine arm *vs.* 54% in the ADT alone arm. Similar to STAMPEDE, the authors noted longer term follow up would be required to assess overall survival (7).

RTOG 0521 is a phase III trial that randomized 612 subjects to standard radiation therapy and ADT with or without docetaxel in subjects with high risk clinically localized prostate cancer. High risk was defined as Gleason ≥9, Gleason 7 or 8 with PSA ≥20 ng/mL or Gleason 8 with PSA <20 ng/mL with ≥T2 disease. Maximum allowed PSA was 150 ng/mL. The initial findings of RTOG 0521 have now been published subsequent to the publication of the Oudard *et al.* study (REF). With median follow up of 5.7 years four-year overall survival was 89% for the control arm *vs.* 93% with the addition of docetaxel (P=0.034 with HR of 69%) based on a prospective one-sided log rank analysis. Six-year rates of distant metastasis and disease free survival were 14% and 9.1% (two sided P=0.044) and 55% and 65% (two sided P=0.043) respectively (8). Longer-term results confirming translation of improvement in disease

free survival and distant metastasis free survival into more definitive overall survival benefit are awaited.

A meta-analysis assessing these three studies failed to demonstrate a significant overall survival benefit to date but did reveal a failure free survival benefit with reduced 4-year failure are of 8%. It remains to be seen whether additional follow-up will yield an improvement in overall survival (10).

While the aforementioned studies have focused on use of radiation as the primary local treatment, NRG GU002 is currently enrolling patients post-prostatectomy with high-risk of failure defined as a PSA nadir of ≥0.2 ng/mL. Subjects are randomized to post-operative RT and ADT with or without adjuvant docetaxel following completion of radiation therapy (6). This trial builds upon a prior single arm study, RTOG 0621 which provided a strong signal as to the potential benefit of docetaxel in high risk patients post-prostatectomy. In particular, patients who did not achieve an undetectable PSA nadir post-prostatectomy had a distinctly worse 3-year rate of progression free survival of 54% as compared to other high risk patients with 92% highlighting the importance of patient selection for more aggressive therapy (11). TAX-3501 was a phase III study designed to assess the benefit of addition of docetaxel to ADT in subjects with high risk disease as defined following radical prostatectomy. Unfortunately this trial closed due to poor accrual (12). This study, opened in 2005 preceded the widespread use of radiation in the post-operative setting, a key difference from RTOG 0621 and NRG GU002.

Taken together these studies have demonstrated modest improvements in treatment outcomes with use of docetaxel in management of high-risk non-metastatic prostate cancer. Longer-term follow-up may very well translate into improved, or in the case of RTOG 0521, greater overall survival advantage. Given the wide range of definitions of high-risk across these studies, additional focus is needed in identifying which patients are most likely to benefit from chemotherapy. In this regard, sub-classification and genomic profiling show great promise in guiding treatment approach. Similar to breast cancer, classification of prostate cancer into luminal A, B or basal sub-type may help direct choice of optimal systemic therapy (13). Several retrospective studies have demonstrated ability of genomic classification to guide treatment decisions (14-16). Presently, NRG GU002 includes a novel prospective assessment of the ability of genomic profiling to identify which patients will benefit from chemotherapy as a secondary objective. Clearly when it comes to prostate cancer, much like other malignancies, a one size fits all approach to treatment is a thing of the past—much like prostate cancer itself will hopefully be in due time.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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