Review Article

Chemotherapy and radiation for prostate cancer

Mark David Hurwitz

Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA, USA

Correspondence to: Mark David Hurwitz, MD. Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA, USA. Email: mark.hurwitz@jefferson.edu.

Abstract: Over the past few decades there is growing appreciation for the role of chemotherapy in treatment of prostate cancer. Initial successful phase III randomized trials in castration resistant prostate cancer (CRPC) have led to additional successful trials in earlier presentations of disease. Given the established role of radiation in management of locally advanced disease and demonstrated efficacy of taxanes in treatment of prostate cancer, optimal combination of radiation and chemotherapy in this patient population has garnered increased attention. Successful phase III trials in this space have given additional stimulus to further exploring combination therapy with radiation. New directions include assessment of additional chemotherapeutic agents including cabazitaxel and PARP inhibitors as well as personalization of therapy with use of genomic testing and other emerging markers to guide therapeutic decisions.

Keywords: Prostate cancer; radiation; chemotherapy; predictive markers

Submitted Dec 11, 2017. Accepted for publication Feb 27, 2018.
doi: 10.21037/tau.2018.03.07
View this article at: http://dx.doi.org/10.21037/tau.2018.03.07

Introduction

Prostate cancer entails a complete spectrum from indolent disease to highly aggressive lethal forms of the disease. While many men will never require treatment of their prostate cancer and others can be cured with local therapy alone, a significant sub-set may achieve cure with combined local and systemic treatment. The first studies to establish benefit of systemic therapy when combined with radiation therapy for men with clinically localized high-risk prostate cancer focused on the addition of androgen deprivation therapy (ADT). Numerous phase III trials now have shown advantages including improved overall survival with the use of ADT in combination with radiation therapy in treatment of clinically localized intermediate to high risk prostate cancer (1-6). Subsequently, studies have explored the ability of chemotherapy to improve outcomes in treatment of prostate cancer. Initial success in treatment of metastatic disease has led to further studies exploring the role of chemotherapy in progressively earlier stages of disease including in combination with radiation therapy.

Chemotherapy for metastatic prostate cancer

In order to appreciate the emerging role of chemotherapy in combination with local therapies such as radiation, it is important to understand the evolution of use of chemotherapy starting with its application in treatment of castration resistant prostate cancer (CRPC) and subsequent application earlier in the disease spectrum. The first chemotherapeutics for prostate cancer, estramustine and mitoxantrone were approved in the United States for routine clinical care in 1981 and 1996 respectively. These approvals were largely based on PSA response and palliative endpoints with no overall survival benefit established (7-11).

The ability of chemotherapy to impact on prostate cancer survival was first defined in CRPC in 2004 and since then additional studies have defined the role of chemotherapy in increasingly earlier scenarios in disease presentation.

In a phase III study conducted by the Southwest Oncology Group (SWOG) in CRPC, docetaxel and estramustine was compared with mitoxantrone and prednisone. The docetaxel and estramustine arm resulted in an increase in overall survival of 17.5 *vs.* 15.6 months (12). Another contemporary multi-institutional phase III study to SWOG 9916, TAX 327 assessed single agent docetaxel without estramustine in comparison with mitoxantrone. One thousand and six men with CRPC were randomized to receive prednisone with either 12 mg/m^2 mitoxantrone every 3 weeks, 75 mg/m^2 docetaxel every 3 weeks, or 30 mg/m^2 docetaxel weekly. Patients receiving docetaxel on the every 3-week regimen had significantly improved overall survival as compared to mitoxantrone, 18.9 *vs.* 16.5 months with a hazard ratio for death of 0.76. Weekly docetaxel did not result in significantly better survival than mitoxantrone (13). The finding of survival advantage with single agent docetaxel therefore provided new impetus for exploring the role of docetaxel in treatment of high-risk localized disease.

Following the establishment of a role for docetaxel in CRPC, subsequent studies explored the role of taxanes in earlier disease presentations. In a large phase III trial, CHAARTED, addition of six cycles of docetaxel to long-term ADT in men with newly diagnosed hormone naïve prostate cancer resulted in a 14-month improvement in median survival of 58 *vs.* 44 months (HR 0.61, P<0.001) (14). GETUG-AFU 15, a smaller phase III study of 385 patients with radiologically proven metastatic disease included randomization to ADT alone or in combination with up to nine cycles of docetaxel given every three weeks. With median follow-up of 50 months, a modest difference in overall survival in favor of docetaxel was observed, 60 *vs.* 54 months, which however was not statistically significant (15).

Primary radiation and chemotherapy

The effectiveness of docetaxel in upfront treatment of very high risk non-metastatic or hormone naïve metastatic prostate cancer has also become apparent in recent years. The STAMPEDE trial included men with either high-risk locally advanced non-metastatic prostate cancer (node-negative, stage 3 or 4, PSA ≥40 ng/mL or Gleason 8–10) or newly diagnosed metastatic disease. The proportion of non-metastatic (M0) to metastatic subjects was 39%/61% including 15% N+ and 24% N0 amongst the M0 patients. Subjects were randomized to standard of care alone, consisting of at least 3 years of ADT with local radiation initially encouraged and subsequently mandated in 2011 for patients with N0M0 disease and optional for patients with N1M0 disease, or combined with either six cycles of docetaxel, 2 years of zoledronic acid, or with both docetaxel and zoledronic acid.

Exact radiation technique was at the discretion of the treating physician. All patients received treatment to the prostate and seminal vesicles with the option of pelvic nodal radiation for patients with negative nodes on axial imaging. Patients with N+ disease received initial pelvic irradiation. 3D conformal radiation or intensity-modulated radiation therapy (IMRT) were allowed. Recommended total dose was 7,400 cGy in 37 fractions to the prostate and seminal vesicles with optional pelvic node dose of 4,600 to 5,000 cGy in 200 cGy fractions. Hypofractionation or dose escalation at the discretion of the treating physician was allowed.

A total of 2,962 hormone naive men were accrued. Planned use of standard of care radiotherapy was similar across groups (28–29%), In patients with non-metastatic disease, 62% received radiotherapy with higher proportions of N0 than N+ patients receiving radiotherapy. With median follow-up of 42 months, there was a 10-month improvement in median overall survival, 77 *vs.* 67 months with the addition of docetaxel. While the greatest difference in survival was seen in metastatic patients, high-risk M0 patients also benefited (16) with a strong failure-free survival benefit.

In a multi-institutional French trial, GETUG 12, patients with treatment-naïve prostate cancer and at least one risk factor (stage T3–T4 disease, Gleason score of ≥8, PSA >20 ng/mL, or pathological node-positive disease) were randomized to either 3 years of treatment with goserelin plus four cycles of docetaxel on day 2 at a dose of 70 mg/m^2 and estramustine 10 mg/kg per day on days 1–5, every 3 weeks, or goserelin alone. All patients underwent a staging pelvic lymph node dissection. Local treatment was decided upon in a multidisciplinary meeting before patient enrolment. Local treatment was given 3 months after the start of systemic treatment. In patients with pathological node-negative disease, it consisted of radiotherapy or prostatectomy. In patients with node positive disease, it consisted of radiotherapy or no local treatment. When radiotherapy was given, a three-dimensional conformal technique was used. A dose of 4,600–5,000 cGy delivered to the seminal vesicles and pelvic lymph nodes (when included) using a conformal four field technique. The radiation dose delivered to the prostate was originally set at 7,000–7,800 cGy in fractions of 200 Gy and subsequently was amended to require a dose of 7,400–7,800 cGy, as the result of new evidence supporting efficacy of dose escalation (17). Both open and laparoscopic prostatectomy was allowed for patients undergoing surgery.

A total of 413 subjects were enrolled including 207 patients to the ADT plus docetaxel and estramustine group and 206 to the ADT only group. Local treatment consisted of radiotherapy for 358 (87%) of 413 patients. Median dose of radiotherapy was 7,400 cGy in each group. A pelvic field was used in 51% of patients in the ADT plus docetaxel and estramustine group and in 50% of patients in the ADT only group. Twenty-five (6%) of 413 patients had a prostatectomy. Local treatment was the treatment planned before randomization for 99% of evaluable patients.

Median follow-up was 8.8 years. Relapse-free survival was improved with addition of chemotherapy with 62% in the ADT plus docetaxel and estramustine group versus 50% in the ADT only group remaining relapse free at eight years, resulting in a hazard ratio of 0.71. Relapse or death occurred in 43% in the ADT plus docetaxel and estramustine group *vs.* 54% in the ADT only group. In the subset of patients who were treated with radiotherapy and had data available, 21% of 151 in the ADT plus docetaxel and estramustine group versus 18% of 143 in the ADT only group reported a grade 2 or higher long-term side effect (P=0.61). No excess second cancers were noted and there were no treatment-related deaths. Neutropenic fever and grade 3–4 thromboembolic events occurred in only 2% of patients. There was no detriment in quality of life at one year in the ADT plus docetaxel and estramustine group (18).

RTOG 9902 was designed to assess whether adjuvant chemotherapy would improve overall survival in addition to radiation therapy and ADT. Subjects were randomized to radiation therapy and ADT with or without adjuvant chemotherapy with paclitaxel, estramustine, and oral etoposide (TEE). The trial included high-risk patients as defined by PSA 20–100 and Gleason score ≥7 or clinical stage ≥T2 and Gleason score ≥8.

Radiation therapy was initiated 8 weeks after start of ADT. CT simulation was recommended but not required. IMRT was not allowed as it was not sanctioned as an option in NCI trials at the time of initiation of RTOG 9902. Patients on both arms received pelvic radiation to a dose of 4,680 cGy in 180 cGy followed by a prostate boost to deliver 2,340 cGy in 180 cGy fractions for a total prostate dose of 7,020 cGy. If the seminal vesicles were involved, an intermediate volume including the prostate and seminal vesicles was treated to 5,580 cGy. Chemotherapy was initiated beginning 28 days after completion of radiation therapy. ADT with LHRH agonist was continued for a total of 24 months including a total of 4 months of oral anti-androgen through completion of radiation therapy.

The trial was opened in 2000 and closed in 2004 due to excess thromboembolic toxicity in the TEE arm with this toxicity attributed to estramustine. A total of 397 patients were randomized. Median follow-up was 9.2 years. Ten-year results for all randomized patients revealed no significant difference between arms in overall survival, biochemical failure, local progression distant metastases or disease-free survival. Ten-year overall survival was 65% *vs.* 63% in the radiation + ADT *vs.* radiation + ADT + TEE arm (P=0.81). Due to accrual of only 397 of the intended 1,440 subject the power to detect a difference in overall survival was reduced from the study designed 90% to 62% (19).

In follow-up to RTOG 9902, RTOG 0521 was designed to assess whether addition of single agent chemotherapy with docetaxel to standard radiation therapy and ADT would result in improved overall survival in the primary treatment of high-risk clinically localized prostate cancer. At the time of trial development, the favorable results of SWOG 9916 and TAX 327 had been reported generating added interest in exploring the role of docetaxel in earlier stages of disease. RTOG 0521 also updated radiation doses and techniques compared with RTOG 9902. IMRT was added as an option during the conduction of the trial. Radiation included treatment of the pelvic lymph nodes to 4,680 cGy followed by boost to the prostate to a total of 7,200–7,560 cGy at 180 cGy per fraction. Seminal vesicles were included to full dose if involved by tumor.

Preliminary results of RTOG 0521 suggest benefit to the addition of docetaxel to radiation therapy and ADT in the non-metastatic high-risk population of patients receiving primary radiation. Five hundred sixty-three eligible subjects were included in an initial report. With median follow-up of 6 years, there was improvement in 4-year overall survival with addition of docetaxel from 89% to 93% as based on a prospectively designed one-sided log rank analysis (P=0.04, HR 0.70) (Sandler 2015). While falling short of the ambitious study goal inclusive of a HR of 0.49, the degree of benefit was similar to other studies demonstrating benefit to novel treatment strategies in prostate cancer. Longer-term results confirming overall survival benefit are awaited (20).

There is potential for greater benefit but also risk of greater toxicity with concurrent radiation and chemotherapy. Researchers at the University of North Carolina reported the results of a single institution phase I study assessing concurrent docetaxel escalated successfully to 20 mg/m^2 weekly with dose escalated IMRT to 7,800 cGy directed to the prostate and seminal vesicles. All patients also received 2 years of ADT with acceptable side effect profile and promising early efficacy results (21). A similar phase I study using cabazitaxel and IMRT to 7,560 cGy was recently completed at Thomas Jefferson University with final results pending (22).

Post-operative radiation and chemotherapy

Radical prostatectomy is associated with excellent outcomes for many prostate cancer patients, A significant portion of patients however will recur locally, distally or both despite prostatectomy. Patients who do recur within 3 years of prostatectomy have been shown to be at much great risk of death from prostate cancer (23). Adjuvant radiation has been shown to mitigate disease progression in randomized phase III trials for men with high risk features such as seminal vesicle involvement, extra-capsular extension or positive margins as demonstrated in three randomized trials assessing observation *vs.* upfront radiation post-prostatectomy (24-26). Additional analyses have defined high risk groups of patients that do poorly even with additional local therapy with post-operative radiation therapy (27,28). In this very high-risk population the role of systemic therapy including both ADT and chemotherapy is in the process of being defined.

SWOG 8794 revealed that the risk of metastasis or death is greater for men with a detectable PSA post-operatively who receive radiotherapy compared to those with an undetectable PSA who receive adjuvant radiation therapy (27). A recent update of the ARO 9602 study confirmed this finding (28). Given the high risk of failure with radiation alone for patients for whom PSA does not become undetectable post-prostatectomy, optimizing systemic therapy in this patient population is important.

Rationale for the use of ADT and chemotherapy in the post-prostatectomy setting builds upon the use of these agents in treatment of clinically localized and more advanced prostate cancer. Studies have included a range of strategies including ADT alone, chemotherapy alone, combined ADT and chemotherapy, chemotherapy, or combined radiation, ADT and chemotherapy. SWOG 9921 was a phase III trial including 993 high-risk post-prostatectomy patients with undetectable PSA randomized to 2 years of ADT +/− six cycles of mitoxantrone. The study was closed in 2007 to further accrual after three cases of acute myelogenous leukemia (AML) were reported of a total of 487 patients in the mitoxantrone treatment arm. No differences were noted in survival with the addition of chemotherapy (29). A follow-up report revealed excellent long-term disease control in the ADT alone arm (30). The role of chemotherapy without further local treatment in high-risk patients post-prostatectomy has also been assessed in two phase II trials with either docetaxel alone (31) or 24 months of ADT with 3–8 week cycles of ketoconazole and doxorubicin for weeks 1, 3, and 5 and estramustine and docetaxel for weeks 2 ,4, and 6 (32). Both trials revealed relatively promising results in regard to efficacy with acceptable side effect profiles noting comparisons between studies are not feasible given the diverse patient populations studied. Of note the question of efficacy of neoadjuvant docetaxel pre-prostatectomy has also been addressed in the phase III setting on CALGB 90203 with results expected in the coming year (33).

RTOG 0621 was the first cooperative group study to assess use of combined ADT, chemotherapy and radiation in the post-prostatectomy setting. This trial was a single arm phase II study designed to provide an initial assessment of docetaxel in addition to ADT and radiation therapy in treatment of men with high-risk features post-prostatectomy. Eligible patients included men with ≥50% risk of progression with radiation alone based on findings from SWOG 8794 including pathologic T3 and Gleason score ≥8 or with PSA nadir ≥0.2 ng/mL and Gleason score ≥7. A high bar was set seeking to define a 20% or greater increase in 3-year freedom from progression (FFP) with the addition of androgen deprivation and docetaxel as compared to adjuvant radiation therapy alone as define by SWOG 8794. Three-year FFP on RTOG 0621 was 73% despite the fact that patients on RTOG 0621 had worse prognostic factors than the historical control group from SWOG 8794, including Gleason score ≥8 in 82% *vs.* 18% and detectable PSA post-prostatectomy in 47% *vs.* 36%. In particular, patients whose PSA failed to nadir post-prostatectomy to undetectable levels did worse than other patients. Three-year FFP was 54.1% in the subset of 37 patients with PSA nadir >0.2 ng/mL as compared to 92% in all other subjects. At time of analysis with median follow-up of 4.4 years 25 biochemical, 11 distant, and no local failures had occurred with 10 of 11 distant failures associated with detectable PSA post-prostatectomy. Three deaths occurred of which two were prostate cancer related. Univariate and multivariate models revealed post-RP PSA was statistically significantly associated with FFP, biochemical and distant failure and Gleason score with biochemical failure on multivariate analysis. Side effects of chemotherapy, including grade 1–2 peripheral neuropathy and grade 3–4 neutropenia were common, however only 3 cases of febrile neutropenia occurred. Late treatment related toxicities included 4 (5%) various CTCv3.0 grade 3 and 2 (3%) cases of grade 4 urinary incontinence (34). While patients with detectable PSA nadir on RTOG 0621 did better than similar historical controls, the high rate of early failure and disease progression in this high-risk group demonstrated there is a timely and compelling need to further define the role of ADT and chemotherapy in a randomized trial for these patients.

NRG GU002 therefore builds upon the findings of RTOG 0621. This is a phase II/III study with a primary objective to assess the benefit of docetaxel as measured by improvement in freedom from progression (phase II) and subsequently metastasis free survival (phase III) when given in combination with radiation and androgen deprivation in treatment of high-risk prostate cancer post-radical prostatectomy (35). Based on the finding from RTOG 0621 that patients who failed to achieve an undetectable nadir where at much greater risk of progression than other previously defined high-risk patients, eligibility includes those with a post-prostatectomy nadir of ≥0.2 ng/mL and Gleason score ≥7. All subjects receive a total of 6 months of ADT including bicalutamide and an LHRH agonist and radiation. Radiation therapy includes pelvic irradiation to 4,680 cGy followed by a prostatic fossa boost to 6,840 cGy. The seminal vesicle remnants or fossa are also treated to full dose if found to be involved at the time of prostatectomy. Both 3D conformal radiation and IMRT are allowed noting that over 80% of patients on RTOG 0621 received treatment with IMRT.

Future directions

New chemotherapeutic approaches

Further advances in the use of chemotherapy in combination with radiation therapy are likely to involve optimization of use of other established agents apart from docetaxel; incorporation of new drugs into clinical use; and better definition of who may benefit from use of specific chemotherapy regimens.

The multi-institutional phase III TROPIC trial defined a role for cabazitaxel in second line treatment of CRPC. Patients who failed treatment with docetaxel were randomized to mitoxantrone or cabazitaxel with the finding of overall all and progression free survival advantage to the use of cabazitaxel (36). The FIRSTANA trial compared cabazitaxel with docetaxel in treatment of chemo-naïve patients with metastatic CRPC and failed to show a difference in either overall or progression free survival (37). The activity of cabazitaxel in earlier stage disease, however, remains to be defined. The phase III PEACE-2 for high-risk localized prostate cancer is addressing use of cabazitaxel with radiotherapy. Primary results are expected in 2019 (38).

PARP inhibitors are an emerging class of agents now starting to be assessed in primary treatment of locally advanced prostate cancer. These agents work by inhibiting DNA repair and therefore their combined use with DNA damaging agents such as radiation is an intriguing therapeutic strategy. Hyperthermia which works in part through inhibition of DNA repair (39,40) and has shown promising results when combined with radiation in treatment of prostate cancer (41) might also enhance the effects of PARP inhibitors. Likewise, intriguing results have been noted in a series of phase II trials with the addition of carboplatin to taxane therapy (42-44). Addition of radiation and/or hyperthermia to platinum drugs is another possible avenue to advance the use of chemotherapy in locally advanced disease (45,46).

Personalized therapy

Multiple approaches to more specific definition of an individual patient's prostate cancer and tools to assess both prognosis and prediction of treatment response are rapidly moving forward towards routine clinical application.

Prostate cancer sub-typing analogous to breast cancer had provided greater understanding of variations in the range of tumor aggressiveness and response to established therapies (47). As an example, luminal B prostate cancer has been associated with poorer prognosis and increased response to more complete androgen deprivation. Similar to breast cancer, sub-typing of prostate cancer is likely to lead to better understandings of who will derive greatest benefit from chemotherapy including in the locally advanced treatment setting.

Genomic analysis is already showing utility in guiding treatment decisions. A novel secondary objective of NRG GU002 is to assess the ability of a genomic classifying test to predict outcomes in this patient population. Decipher Post-Op is a 22-gene-based signature which was previously developed, from an unbiased transcriptome-wide analysis of prostate cancer samples, to predict for poor clinical outcomes in a cohort of 545 patients with higher-risk disease treated with prostatectomy (48). Subsequently, Decipher was validated to predict disease recurrence and metastases in several studies, and has now been associated with outcomes in over 1,600 patients treated with prostatectomy (49-55). Moreover, recent studies have suggested that Decipher can predict which patients will have poor outcomes following post-operative radiation therapy (53,56-58). A recent multi-institutional study revealed only Decipher and persistently elevated PSA post-prostatectomy were prognostic for metastases. Furthermore, within the group of men with persistently detectable PSA, the 5-year metastasis rate was 1% for Decipher low/intermediate and 24% for Decipher high-risk (P<0.001) (58). Decipher has therefore been incorporated as a stratification critera (low/average *vs.* high Decipher score) along with Gleason score 7 *vs.* 8–10 and 0.2≤ PSA ≤ 1 *vs.* ≥1 ng/mL.

A number of other markers have shown promise in guiding decisions about the use of chemotherapy in prostate cancer. Other avenues of active investigation include circulating tumor cells (59-61), Plasma-free circulating DNA (62), cytokines (63), telomerase activity (64), AR nuclear localization (65,66), and ERG (67).

Conclusions

There is accumulating evidence that chemotherapy when combined with radiation and typically ADT as well has meaningful clinical impact in locally advanced prostate cancer. The use of chemotherapy in this patient population builds upon the demonstrated advantages including survival advantage with docetaxel seen in metastatic disease. New chemotherapeutics coupled with emerging predictive makers and tools promise to further advance treatment in targeted ways to the benefit of many prostate cancer patients.

Acknowledgements

None.

Footnote

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

References

1. Lawton CA, Winter K, Grignon D, et al. Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31. J Clin Oncol 2005;23:800-7. Erratum in: J Clin Oncol 2005;23:8921.
2. Roach M 3rd, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol 2008;26:585-91.
3. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295-300.
4. D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004;292:821-7.
5. Denham JW, Steigler A, Lamb DS, et al. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. Lancet Oncol 2005;6:841-50.
6. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11:1066-73.
7. Eisenberger MA, Simon R, O'Dwyer PJ, et al. A reevaluation of nonhormonal cytotoxic chemotherapy in the treatment of prostatic carcinoma. J Clin Oncol 1985;3:827-41.
8. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormoneresistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996;14:1756-64.
9. Berry W, Dakhil S, Modiano M, et al. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. J Urol 2002;168:2439-43.
10. Albrecht W, Van Poppel H, Horenblas S, et al. Randomized phase II trial assessing estramustine and vinblastine combination chemotherapy vs estramustine alone in patients with progressive hormone-escaped metastatic prostate cancer. Br J Cancer 2004;90:100-5.
11. Hahn NM, Marsh S, Fisher W, et al. Hoosier Oncology Group randomized phase II study of docetaxel, vinorelbine, and estramustine in combination in hormone-

refractory prostate cancer with pharmacogenetic survival analysis. Clin Cancer Res 2006;12:6094-9.
12. Petrylak DP, Tangen CM, Hussain M, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513-20.
13. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-12.
14. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737-46.
15. Gravis G, Boher JM, Joly F, et al. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol 2016;70:256-62.
16. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronicacid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163-77.
17. Zaorsky NG, Palmer JD, Hurwitz MD, et al. What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation. Radiother Oncol 2015;115:295-300.
18. Fizazi K, Faivre L, Lesaunier F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. Lancet Oncol 2015;16:787-94.
19. Rosenthal SA, Hunt D, Sartor AO, et al. A phase 3 trial of 2 years of androgen suppression and radiation therapy with or without adjuvant chemotherapy for high risk prostate cancer: final results of radiation therapy oncology group phase 3 randomized Trial NRG Oncology RTOG 9902. Int J Radiat Oncol Biol Phys 2015;93:294-302.
20. Sandler HM, Hu C, Rosenthal SA, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521). J Clin Oncol 2015;33:Abstr LBA5002.
21. Chen RC, Rosenman JG, Hoffman LG, et al. Phase I study of concurrent weekly docetaxel, high-dose intensity-modulated radiation therapy (IMRT) and androgen-deprivation therapy (ADT) for high-risk prostate cancer. BJU Int 2012;110:E721-6.
22. Cabazitaxel with radiation and hormone therapy for prostate cancer. ClinicalTrials.gov Identifier: NCT01420250. Available online: https://clinicaltrials.gov/ct2/show/NCT01420250
23. Freedland SJ, Humphreys EB, Mangold LA, et al. Time to PSA Recurrence afterradical prostatectomy and the risk of prostate cancer specific mortality. J Urol 2006;176:1404-8.
24. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant Radiotherapy for Pathologic T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-term Followup of a Randomized Clinical Trial. J Urol 2009;181:956-62.
25. Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005;366:572-8.
26. Wiegel T, Bottke D, Willich N, et al. Phase III results of adjuvant radiotherapy (RT) versus "wait and see" (WS) in patients with pT3 prostate cancer following radical prostatectomy (RP) (ARO96-02/AUO AP 09/95). J Clin Oncol 2005;23:4513.
27. Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: Analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol 2007;25: 2225-9.
28. Wiegel T, Bartkowiak D, Bottke D. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of the ARO 96-02 trial. Int J Radiat Oncol Biol Phys 2015;91:288-94.
29. Flaig TW, Tangen CM, Hussain MH, et al. Randomization reveals unexpected acute leukemias in Southwest Oncology Group prostate cancer trial. J Clin Oncol 2008;26:1532-6.
30. Dorff TB, Flaig TW, Tangen CM, et al. Adjuvant androgen deprivation for high-risk prostate cancer after radical prostatectomy: SWOG S9921 study. J Clin Oncol 2011;29:2040-5.
31. Kibel AS, Rosenbaum S, Kattan MW, et al. Adjuvant weekly docetaxel for patients with high risk prostate cancer after radical prostatectomy: a multi-institutional pilot study. J Urol 2007;177:1777-81.
32. Amato R, Stepankiw M, Gonzales P. A phase II trial of androgen deprivation therapy (ADT) plus chemotherapy as initial treatment for local failure or advanced prostate cancer. Cancer Chemother Pharmacol 2013;71:1629-34.
33. Surgery with or without docetaxel and leuprolide or

goserelin in treating patients with high-risk localized prostate cancer. Alliance for Clinical Trials in Oncology. ClinicalTrials.gov Identifier: NCT00430183. Available online: https://clinicaltrials.gov/ct2/show/NCT00430183
34. Hurwitz MD, Harris J, Sartor O, et al. Adjuvant radiation therapy, androgen deprivation, and docetaxel for high-risk prostate cancer postprostatectomy: Results of NRG Oncology/RTOG study 0621. Cancer 2017;123:2489-96.
35. Antiandrogen Therapy and Radiation Therapy With or Without Docetaxel in Treating Patients With Prostate Cancer That Has Been Removed by Surgery. Available online: https://clinicaltrials.gov/ct2/show/NCT03070886
36. De Bono JS, Hardy-Bessard AC, Kim CS, et al. Phase III non-inferiority study of cabazitaxel (C) 20 mg/m2 (C20) versus 25 mg/m2 (C25) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D). J Clin Oncol 2016;34:5008.
37. Sartor O, Oudard S, Sengelov L, et al. Cabazitaxel vs docetaxel in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: a three-arm phase III study (FIRSTANA). J Clin Oncol 2016;34:5006.
38. A Phase III of Cabazitaxel and Pelvic Radiotherapy in Localized Prostate Cancer and High-risk Features of Relapse (PEACE2). Available online: https://clinicaltrials.gov/ct2/show/NCT01952223
39. Krawczyk PM, Eppink B, Essers J, et al. Mild hyperthermia inhibits homologous recombination, induces BRCA2 degradation, and sensitizes cancer cells to poly (ADP-ribose) polymerase-1 inhibition. Proc Natl Acad Sci U S A 2011;108:9851-6.
40. Oei AL, Vriend LE, Crezee J, et al. Effects of hyperthermia on DNA repair pathways: one treatment to inhibit them all. Radiat Oncol 2015;10:165.
41. Hurwitz MD, Hansen JL, Prokopios-Davos S, et al. Hyperthermia combined with radiation for the treatment of locally advanced prostate cancer: long-term results from Dana-Farber Cancer Institute study 94-153. Cancer 2011;117:510-6.
42. Oh WK, Halabi S, Kelly WK, et al. A phase II study of estramustine, docetaxel, and carboplatin with granulocyte-colony-stimulating factor support in patients with hormone-refractory prostate carcinoma: Cancer and Leukemia Group B 99813. Cancer 2003;98:2592-8.
43. Ross RW, Beer TM, Jacobus S, et al. A phase 2 study of carboplatin plus docetaxel in men with metastatic hormone-refractory prostate cancer who are refractory to docetaxel. Cancer 2008;112:521-6.
44. Corn PG, Tapia ELN, Xiao L, et al. Confirmatory analysis to determine associations between platinum-sensitivity, molecular signature of combined tumor suppressor defects and aggressive variant prostate carcinomas (AVPC). J Clin Oncol 2016;34;5020.
45. Hahn GM. Potential for therapy of drugs and hyperthermia. Cancer Res 1979;39:2264-8.
46. Herman TS, Teicher BA. Sequencing of trimodality therapy [cis-diamminedichloroplatinum(II)/hyperthermia/radiation] as determined by tumor growth delay and tumor cell survival in the FSaIIC fibrosarcoma. Cancer Res 1988;48:2693-7.
47. Zhao SG, Chang SL, Erho N, et al. Associations of luminal and basal subtyping of prostate cancer with prognosis and response to androgen deprivation therapy. JAMA Oncol 2017;3:1663-72.
48. Erho N, Crisan A, Vergara IA, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PLoS One 2013;8:e66855.
49. Karnes RJ, Bergstralh EJ, Davicioni E, et al, Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol 2013;190:2047-53.
50. Tomlins SA, Alshalalfa M, Davicioni E, et al. Characterization of 1577 primary prostate cancers reveals novel biological and clinicopathologic insights into molecular subtypes. Eur Urol 2015;68:555-67.
51. Klein EA, Yousefi K, Haddad Z, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. Eur Urol 2015;67:778-86.
52. Den RB, Feng FY, Showalter TN, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. Int J Radiat Oncol Biol Phys 2014;89:1038-46.
53. Freedland SJ, Choeurng V, Howard L, et al. Utilization of a genomic classifier for prediction of metastasis following salvage radiation therapy after radical prostatectomy. Eur Urol 2016;70:588-96.
54. Ross AE, Johnson MH, Yousefi K, et al. Tissue-based genomics augments post-prostatectomy risk stratification in a natural history cohort of intermediate- and high-risk men. Eur Urol 2016;69:157-65.
55. Glass AG, Leo MC, Haddad Z, et al. Validation of a genomic classifier for predicting post-prostatectomy recurrence in a community based health care setting. J Urol 2016;195:1748-53.

56. Den RB, Yousefi K, Trabulsi EJ, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. J Clin Oncol 2015;33:944-51.
57. Prensner JR, Zhao S, Erho N, et al. RNA biomarkers associated with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SChLAP1. Lancet Oncol 2014;15:1469-80.
58. Spratt DE, Dai DLY, Den RB, et al. Performance of a prostate cancer genomic classifier in men with PSA persistence post-prostatectomy. Eur Urol 2018;74:107-14.
59. de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration resistant prostate cancer. Clin Cancer Res 2008;14:6302-9.
60. Scher HI, Jia X, de Bono JS, et al. Circulating tumor cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. Lancet Oncol 2009;10:233-9.
61. Goldkorn A, Ely B, Quinn DI, et al. Circulating tumor cell counts are prognostic of overall survival in SWOG S0421: a phase III trial of docetaxel with or without atrasentan for metastatic castration-resistant prostate cancer. J Clin Oncol 2014;32:1136-42.
62. Mehra N, Christova R, Pope L, et al. Association of plasma cell-free DNA concentration (cfDNA) with outcome from taxane therapy (TT) for castration resistant prostate cancer (CRPC). J Clin Oncol 2016;34:5014.
63. Mahon KL, Lin HM, Castillo L, et al. Cytokine profiling of docetaxel resistant castration-resistant prostate cancer. Br J Cancer 2015;112:1340-8.
64. Goldkorn A, Ely B, Tangen CM, et al. Circulating tumor cell telomerase activity as a prognostic marker for overall survival in SWOG 0421: a phase III metastatic castration resistant prostate cancer trial. Int J Cancer 2015;136:1856-62.
65. Tagawa ST, Antonarakis ES, Saad F, et al. TAXYNERGY: randomized phase II trial of early switch from first-line docetaxel to cabazitaxel or vice versa with CTC biomarkers in patients with mCRPC who have not received prior chemotherapy. J Clin Oncol 2016;34:5007.
66. DarshanMS, LoftusMS, Thadani-Mulero M, et al. Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses inmetastatic prostate cancer. Cancer Res 2011;71:6019-29.
67. Galletti G, Matov A, Beltran H, et al. ERG induces taxane resistance in castration-resistant prostate cancer. Nat Commun 2014;5:5548.

Cite this article as: Hurwitz MD. Chemotherapy and radiation for prostate cancer. Transl Androl Urol 2018;7(3):390-398. doi: 10.21037/tau.2018.03.07

