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Changing Perspectives of the Role of Chemotherapy in Advanced Prostate Cancer

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The use of cytotoxic chemotherapy in advanced prostate adenocarcinoma has been validated by the recent demonstration of survival benefit in two large randomized phase III trials [1,2]. Before publication of these landmark trials, SWOG 9916 and TAX 327, no chemotherapeutic regimen had shown survival benefit in the treatment of androgen independent prostate cancer (AIPC). These trials provide new encouragement for the use of chemotherapy in all stages of disease. Improved communication between medical and urologic oncologists and early patient referral for clinical trial participation remains essential for identifying new chemotherapeutic regimens with improved activity in AIPC and for defining the role of chemotherapy in earlier-stage disease. This article discusses the role of chemotherapy as the current standard of care for the treatment of AIPC and provides a historical perspective of the trials that preceded the development of current docetaxel-based regimens.

Chemotherapy for AIPC

Trials from the National Prostatic Cancer Project era

In the 1980s, the National Prostatic Cancer Project (NPCP) conducted the largest series to date of phase II trials involving single and combinational cytotoxic agents in AIPC. The results of the NPCP and other early trials have previously been reviewed and heavily criticized for erroneously concluding that many of the tested agents possessed clinically significant activity [3–6]. Although the trials were not designed to study impact on survival, patient median survival was generally no better than best supportive care, even though the response rates often exceeded 50% with some regimens. The underlying biology and difficulties associated with studying advanced prostate cancer can explain the misleading conclusions drawn from some of the trials. The classic objective criteria for gauging tumor response in phase II trials continue to be bidimensional measurement of solid tumor lesions before and after therapy. Because prostate cancer often metastasizes to bone only, assessment of tumor response after therapy in AIPC has been difficult to achieve in an objective and reproducible manner. Imaging modalities do not provide accurate bidimensional measurement of skeletal lesions, and, before the routine use of serum prostate specific antigen (PSA) as a surrogate marker, the methodologic challenges of measuring tumor response were well recognized. Faced with these limitations, the NPCP-era trial investigators used response criteria that were often subjective and that lacked the specificity to provide accurate assessment of drug activity. For example, the presence of "stable" disease, as defined by the absence of progression on bone scan and acid phosphatase levels after 12 weeks of therapy, was included as one criterion for drug response in the NPCP guidelines [7]. The trials did show that patients who had "stable" disease had longer median survival than those who had progressed, but they did not distinguish whether disease stability was a result of treatment or reflected the underlying biology of

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disease in those patients [8]. In the NPCP trials, approximately 90% of the patient responses were classified as "stable disease" [4]. Because this response criterion is hardly specific for drug effect, false "activity" was incorrectly attributed to drugs that ultimately were shown to lack clinical benefit.

Mitoxantrone

After the NPCP and other trials of the 1980s, much debate existed over how best to measure tumor response in AIPC clinical trials. At the time, the general attitude regarding the use of chemotherapy in this setting was pessimistic and shared by urologists and oncologists alike. However, in the 1990s, the use of post-treatment serum PSA decline was validated as a surrogate marker for drug activity, and trialists were hopeful that PSA response could provide a much needed objective criterion that was reproducible and could be used in patients who had isolated skeletal disease [9,10]. Measurement of PSA response, as defined by a $>50\%$ decline from pretreatment baseline, solved key problems from earlier trials and established an end point in subsequent trials that more accurately reflected drug activity.

After acknowledgment of limited response criteria before the routine use of PSA decline, investigators considered palliation of symptoms as a primary endpoint in trials of cytotoxic agents. The idea originated in the AIPC setting after low-dose prednisone was shown to improve pain symptoms and quality of life [11]. Although PSA response has limitations, its superiority over historical standards quickly established this criterion as a gold standard for drug activity in phase II trials. Mitoxantrone, a member of the anthracenedione class that interacts with DNA topoisomerase II, was selected for evaluation of palliative ability based on a favorable side effect profile in elderly patients from an earlier phase II study [12–14]. Based on palliative endpoints, two phase III trials established that the addition of mitoxantrone provided superior response over glucocorticoids alone [15–17]. Mitoxantrone subsequently became the first cytotoxic agent approved by the FDA for use in AIPC and was approved for palliative treatment based on these trials. After FDA approval, mitoxantrone remained first-line standard of care in symptomatic patients before the approval of docetaxel.

Mitoxantrone provides effective palliative therapy. Although PSA response rates ranged from 33% to 48% in three phase III trials, a survival advantage over best supportive care has never been shown [16–18]. Additional phase II trials have explored the feasibility of mitoxantrone in combination with other cytotoxic agents or as sequential therapy with docetaxel-based regimens [19–23]. However, many of these studies accrued taxane-naive patients and need to be re-evaluated because docetaxel has been approved as first-line therapy. Recent trials have also studied the use of mitoxantrone in the second-line setting after patients have failed initial taxane therapy, although data suggest limited activity [24–26]. Based on the promise of docetaxel-based regimens (see below), the role of mitoxantrone will likely continue to diminish.

Estramustine

Estramustine is a synthetic conjugate of estradiol and a nitrogen mustard that was rigorously studied in the NPCP trials and found to have modest activity [4,27]. Although the drug was designed to target delivery of the mustard conjugate to malignant cells that overexpressed sex hormone receptors, estramustine acts through binding microtubule-associated proteins and inducing microtubule destabilization [27,28]. Preclinical studies suggest that combination of estramustine with other antimicrotubule agents could potentiate a cytotoxic effect in vivo [29,30]. These observations provided the scientific rationale for a large number of clinical studies of estramustine combined with other antimicrotubule agents. Many of these trials consistently showed that the addition of estramustine improved PSA response rates over single-agent therapy in the phase II setting [31–49]. Finally, the activity of an estramustine-containing doublet was definitively established by the SWOG 9916 phase III trial, which reported a prolongation of survival in patients who had AIPC treated with docetaxel and estramustine (D/E). SWOG 9916 was not designed to evaluate the contribution of each drug to the regimen. The TAX 327 phase III trial evaluating the docetaxel/prednisone (D/P) doublet showed a similar survival benefit in the docetaxel-treated arm. The results from the TAX 327 trial (see below) suggest that the efficacy of estramustine in the D/E doublet is limited and that the survival benefit is primarily due to docetaxel.

Estramustine is associated with the development of thromboembolic events in up to 25% of treated individuals [50]. Despite this risk, interest

in combining the drug with other agents persists [19,51–53]. Many of these trials were written before the results of TAX 327 and SWOG 9916 were known. Given the risk for thromboembolism and limited contribution to docetaxel-based regimens, the continued use of estramustine must be questioned.

Taxanes

In the combination phase II studies involving estramustine, the taxanes had some of the highest activity among the classes tested. The early-phase trials involving paclitaxel and docetaxel have previously been reviewed in detail and are summarized here [54]. Single-agent paclitaxel has shown limited activity in AIPC, with PSA response ranging from 0% to 39% and measurable disease responses ranging from 4% to 50% depending on the administration schedule [55,56]. In these studies, weekly dosing provided better response rates than every-3-week administration, although 33% of patients experienced grade 3 neuropathy [55].

Based on the synergism observed in preclinical models [29], multiple phase II studies evaluated response rates of the paclitaxel/estramustine (P/E) doublet [35–38]. One study combined 96-hour paclitaxel infusion every 3 weeks with oral estramustine and reported a 53% PSA response rate without any grade 3 neuropathy [35]. This study provided evidence that optimized paclitaxel dosing combined with estramustine could produce meaningful responses without excess toxicity. Other trials using lower doses of weekly paclitaxel in combination with estramustine observed PSA response rates ranging 42% to 60% with significantly less grade 3 neuropathy than the original single-agent study [37,38]. Higher-dose weekly paclitaxel in combination with estramustine failed to improve outcome in one trial that reported a 62% PSA response accompanied by grade 3 neuropathy in 21% of patients [36].

Docetaxel is a semisynthetic taxane that has been shown to have greater preclinical activity than paclitaxel [57]. Single-agent phase II studies have been conducted using weekly and every-3-week dosing schedules. In two studies, every-3-week dosing resulted in PSA response rates of 38% to 46%, and one of the studies reported a median survival of 27 months [58,59]. Three trials examined weekly administration of docetaxel and reported PSA response rates ranging from 41% to 48%, with median survival ranging from 9 to 20 months [60–62].

In general, single-agent docetaxel phase II studies showed improved activity and toxicity profiles over single-agent paclitaxel. Because the addition of estramustine to paclitaxel improved response rates in phase I/II trials, the combination of estramustine and docetaxel has also been examined. One small trial based on a weekly dosing schedule reported a 72% PSA response rate with median survival of 16 months, which suggested that, like paclitaxel, the addition of estramustine to docetaxel may provide better response rates than docetaxel alone [63]. Grade 1–3 neutropenia was noted to be 17% in this study. Alternatively, phase I/II D/E doublets based on every-3-week dosing have shown PSA responses of 45% to 74%, measurable soft tissue response rates from 20% to 57%, and a median survival reported in two trials to be 20 to 23 months [32,33,64–66]. Grade 3–4 neutropenia ranged from 56% to 75% in these studies. Although greater myelosuppression was observed in studies based on every-3-week docetaxel administration, rates of neutropenic fever were low. These early docetaxel trials seemed to favor every-3-week administration, and the superiority of every-3-week dosing was clearly established in the two pivotal phase III trials discussed below.

SWOG 9916

In October 2004, two randomized phase III trials concurrently reported a modest survival advantage from docetaxel-based therapy in AIPC [1,2]. These trials ushered in a new era of excitement for the use of cytotoxic regimens because they marked the first time any chemotherapeutic agent has demonstrated a survival advantage in this disease setting. SWOG 9916 [2] was the first of these trials that compared D/E against the previous standard of care mitoxantrone and prednisone (M/P). The significant activity of D/E noted in combination phase I/II trials mentioned previously served as the basis for this trial. Overall survival was the primary endpoint, and the trial was powered to detect a 33% survival improvement in the D/E arm over the M/P arm. Progression-free survival, PSA, and measurable response rates were secondary endpoints. Patients were randomized to receive one of the following 21-day regimens: (1) estramustine 280 mg three times a day on days 1 through 5, docetaxel 60 mg/m^2 on day 1 and 60 mg of dexamethasone over three divided doses starting the night before docetaxel; or (2) mitoxantrone 12 mg/m^2 on day 1 plus

prednisone 5 mg twice daily. Doses were increased to docetaxel 70 mg/m^2 and mitoxantrone 14 mg/m^2 on subsequent cycles if no grade 3–4 toxicities were noted in the initial cycle.

Of the 674 eligible patients in the study, 338 received D/E, and 336 received M/P. The median patient age was 70 years, and approximately 90% of both arms were SWOG performance status 0 or 1. The median PSA (ng/ml) was 84 and 90 in the D/E and M/P arms, respectively. Bone pain less than grade 2 was reported in 64% of both arms. Although the study did not achieve the primary endpoint of demonstrating a 33% improvement in survival between the two treatment arms, intention-to-treat analysis revealed a median survival of 17.5 months among patients receiving D/E and 15.6 months among patients receiving M/P ($P = .02$). Along with the TAX 327 trial discussed below, the 2-month median survival advantage noted in this study represented the first survival benefit from chemotherapy in patients with AIPC. The hazard ratio for death in this trial was 0.8 (95% confidence interval, 0.67–0.97), so during the study, the risk of death was reduced by 20% in the docetaxel-treated group. Analysis of secondary endpoints further supported the advantage of D/E therapy: Median time to progression was 6.3 months in the D/E arm versus 3.2 months in the M/P arm ($P < .001$). PSA response rates were 50% in D/E group and 27% in M/P group ($P < .001$). Partial response of measurable disease and subjective pain relief rates were not statistically different between the two treatment groups. Withdrawal rates for adverse events were 16% in the D/E arm and 10% in the M/P arm. Eight and four treatment-related deaths occurred in the D/E and M/P arms, respectively. Grade 3–4 neutropenia occurred in 12.5% versus 16.1% of patients in the M/P and D/E arms, respectively, although the difference was not statistically significant ($P = .22$). The rate of severe neutropenia in patients treated with D/E was markedly lower than seen in the earlier-phase trials, and the rate of neutropenic fever was only 5% in this group.

The results from SWOG 9916 showed that combination of docetaxel and estramustine prolongs median survival by 2 months and reduces the risk for death relative to mitoxantrone and prednisone. The median survival of 15.6 months in the control group was approximately 3.5 months longer than reported in earlier phase III trials that studied a similar regimen of mitoxantrone and prednisone [16,17]. Higher tumor burden in the patients of the earlier trials may account for this difference because the previously studied patients had symptomatic disease and slightly higher median PSA values (150–158 ng/ml). Nonetheless, the SWOG 9916 trial definitively established that docetaxel-based therapy every 3 weeks prolongs median survival and reduces the risk of death. These results were complemented by the TAX 327 trial and immediately set a new standard of care for first-line therapy in patients who have AIPC.

TAX 327

The TAX 327 trial, reported concurrently with SWOG 9916, was a randomized phase III study that compared dose-equivalent docetaxel given on a weekly basis or every 3 weeks with prednisone against mitoxantrone given every 3 weeks [1]. Notable differences of this trial compared with SWOG 9916 include the addition of a weekly docetaxel arm and the absence of estramustine in the docetaxel arms. As in the SWOG trial, the primary endpoint of this study was to detect an overall survival advantage in the docetaxel arm compared with the mitoxantrone control arm. Secondary endpoints in this trial differed slightly and included measurement of pain levels, quality of life (measured by the FACT-P questionnaire), PSA, and measurable soft tissue responses. Like the SWOG trial, inclusion criteria required progressive AIPC measured radiographically and biochemically, ongoing androgen-ablation therapy, and prior cessation of antiandrogen therapy. Patients were randomized to receive one of the following treatment regimens: (1) docetaxel 75 mg/m^2 every 3 weeks (D/P), (2) docetaxel 30 mg/m^2 every week (wD/P), or (3) mitoxantrone 12 mg/m^2 every 3 weeks (M/P). All patients received prednisone 5 mg twice daily, and patients receiving docetaxel were premedicated with dexamethasone. The impact of dexamethasone on treatment response in the docetaxel arms has previously been suggested not to contribute to the treatment response [67].

Of the 1006 patients enrolled in the trial, 332, 330, and 335 were treated with D/P, wD/P, and M/P, respectively. In each of the three arms, the median patient age was 68 to 69 years, and 12% to 14% of patients had Karnofsky performance status <80%. The median serum PSA value in the three treatment arms ranged from 108 to 123 ng/ml, and approximately 45% of patients had pain. Ninety percent of patients had known

bone metastases, and 40% had measurable soft-tissue lesions. Based on intention-to-treat analysis, the median durations of survival were 18.9 months in the every-3-week docetaxel arm, 17.4 months in the weekly docetaxel arm, and 16.5 months in the mitoxantrone arm. Only the every-3-week docetaxel regimen was demonstrated to have a statistically significant survival benefit compared with mitoxantrone. The hazard ratio for death using this regimen was 0.76 (95% confidence interval, 0.62–0.94), which confirmed the mortality reduction seen in the SWOG trial with every-3-week docetaxel/estramustine. Analysis of secondary endpoints showed reduced pain in 35% ($P = .01$), 31% ($P = .08$), and 22% of patients treated with D/P, wD/P, and M/P, respectively. Quality of life improvement was noted in 22% ($P = .009$), 23% ($P = .005$), and 13% of patients treated with D/P, wD/P, and M/P, respectively. D/P provided superior palliation relative to the prior standard M/P, whereas, pain reduction in patients treated with weekly D/P was not different from those treated with M/P. Based on these results, the use of weekly D/P for palliative intent only may be appropriate if the toxicity profile precludes use of every-3-week docetaxel. However, based on the survival advantage, every-3-week docetaxel is the preferred first-line standard regimen. The PSA response to treatment was 45% ($P < .001$) in the D/P, 48% ($P < .001$) in the wD/P, and 32% in the M/P arms (see below). Grade 3–4 neutropenia was seen in 32% ($P \leq .05$) of patients treated with D/P, in 2% ($P \leq .0015$) of patients treated with wD/P, and in 35% of patients treated with M/P, although only 3% of D/P-treated patients had febrile neutropenia. Common adverse events with D/P that occurred more frequently with every-3-week administration included fatigue, diarrhea, alopecia, and neuropathy. Three of five treatment-related deaths occurred in the mitoxantrone group.

The results of TAX 327 confirmed the findings of SWOG 9916 by demonstrating a 2-month survival advantage and a 20% mortality reduction over the study period in patients who had AIPC treated with docetaxel every 3 weeks. Weekly docetaxel was not associated with a statistically significant survival advantage, although this regimen demonstrated pain reduction equivalent to the historical standard of mitoxantrone and prednisone. Every-3-week docetaxel was accompanied by a slightly worse toxicity profile than mitoxantrone and prednisone, although treatment-related deaths were essentially the same in all arms. The survival advantage associated with every-3-week docetaxel reported in the TAX 327 and SWOG 9916 trials represent independent confirmation from two large, randomized phase III trials that cytotoxic chemotherapy with an acceptable toxicity profile can prolong life in patients with AIPC. These two trials provide new excitement for the use of cytotoxic chemotherapy in patients who have AIPC and establish a foundation on which to develop improved regimens. The urologist will continue to play a critical role in defining better cytotoxic regimens by early referral to medical oncologists for participation in clinical trials. Although these trials report a modest survival improvement, they herald greater potential activity with future regimens. Many trials have been designed based on the results of TAX 327 and SWOG 9916, and expectations for future survival gains in AIPC are optimistic.

PSA response as surrogate marker for clinical benefit

Post-treatment serum PSA decline of at least 50% of pretreatment baseline has been suggested as a surrogate marker of survival benefit in phase II trials [9,10,68,69]. One interesting observation from the TAX 327 trial is the failure of PSA response to predict the proven survival advantage. Only 45% of patients in the every-3-week docetaxel arm experienced a post-therapy PSA decline of at least 50% despite a 2.4-month prolongation of survival. Follow-up analysis by the TAX 327 investigators further confirmed that the PSA response only partly explained the observed survival benefit [70]. Because 50% of patients treated with D/E in SWOG trial had at least a 50% reduction in post-treatment PSA, these results suggest that the addition of estramustine serves only to improve PSA response rates without additive survival benefit. This suggestion is supported by a recent randomized phase II study comparing every-3-week docetaxel with docetaxel plus estramustine that showed a PSA response in 68% of patients treated with D/E compared with only 29% of those treated with docetaxel alone [71]. Based on PSA response, results from this phase II trial imply that every-3-week D/E should have far greater clinical benefit than docetaxel alone and that every-3-week docetaxel alone should not produce any survival benefit. The results of TAX 327 prove otherwise and highlight an important limitation with the use of post-treatment PSA decline as a surrogate marker in phase II studies.

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