Chemotherapy for non-hormone refractory prostate cancer

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Introduction: *Randomized clinical trials (RCTs) have demonstrated the benefits of chemotherapy for hormone-refractory prostate cancer (HRPC). These data have intensified interest in the use of chemotherapy for non-HRPC. Chemotherapy plus androgen deprivation therapy (ADT) is now under study in a number of RCTs in hormone-naïve patients.*
Materials and methods: *Important data supporting the intuitive, preclinical and clinical rationale for study of chemotherapy plus ADT in non-HRPC were identified and narratively reviewed.*
Results: *There is evidence that chemotherapy can improve survival in HRPC. Chemohormonal therapy reduces recurrence in premenopausal women with estrogen receptor-positive early breast cancer, a group analogous to men with localized prostate cancer. Preclinical data supports earlier use of use of chemotherapy plus ADT simultaneously rather than sequentially. Some RCTs suggest disease control is improved by this approach in non-HRPC. A large single arm trial of docetaxel plus ADT prior to radical prostatectomy has demonstrated safety, feasibility, and evidence of efficacy.*
Conclusions: *There is sufficient rationale for studying chemotherapy in combination with ADT in non-HRPC. Large scale RCTs investigating this are imminent for men with high-risk localized disease, with biochemical recurrence after local therapy, and with hormone-naïve metastatic disease.*

Key Words: prostatic neoplasms, drug therapy, clinical trials

Introduction

Chemotherapy is now established as a standard treatment option for palliation of symptoms and suppression of disease activity in men with metastatic hormone-refractory prostate cancer (HRPC) on the basis of results from randomized controlled clinical trials (RCTs). RCTs have also identified a modest overall survival benefit in men with HRPC treated with docetaxel in comparison to mitoxantrone.[1,2] These data have provided additional clinical rationale and intensified interest in the study of chemotherapy earlier in the natural history of prostate cancer. Specifically, the addition of chemotherapy agents, and docetaxel in particular, to androgen deprivation therapy (ADT) is now under study in a number of RCTs in hormone-naïve patients with metastatic disease, biochemical failure following local therapy, and in combination with prostatectomy or radiotherapy in high-risk patients.

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Intuitive rationale

The hypothesis that drug therapy active in incurable metastatic solid tumors can potentially effect cure when used earlier in their natural history of solid

tumors is well tested. This paradigm has led to the identification of effective chemotherapy and increased cure rates in localized breast, colorectal, and lung cancers. ADT has been used for palliation and disease control in metastatic prostate cancer for over half a century, and more recently has been demonstrated to improve survival after local therapies.[3,4] Is there much to gain from the use of chemotherapy in prostate cancer, perhaps the most hormone-sensitive of all solid tumors?

Evidence from other hormone-sensitive cancers suggests that chemotherapy may provide additional benefits beyond hormonal therapy alone. Men with newly diagnosed prostate cancer usually have physiologically significant levels of androgens as well as tumors that uniformly express the androgen receptor. By analogy, the biology of tumor and host correspond to premenopausal breast cancer patients, who also have physiologically significant levels of estrogens along with estrogen-receptor expressing tumors. In an individual patient data meta-subanalysis including 2254 of these patients with early breast cancer treated in RCTs, the Early Breast Cancer Trialists' Group has shown that the addition of polychemotherapy to tamoxifen in this group reduced breast cancer recurrence from 21.6% to 14.0% (absolute reduction of 7.6%).[5] Although possibly in part due to ovarian suppression, the magnitude of this effect suggests an additive effect of chemotherapy combined with hormonal therapy.

The curative potential of adjuvant chemotherapy is predicated on the availability of active chemotherapy in the metastatic setting. Recently published RCTs provide such evidence for the taxane drug, docetaxel. In 1006 men with metastatic HRPC, Tannock et al[1] reported superior palliative and prostatic-specific antigen (PSA) response rates with docetaxel-prednisone given weekly and every 3 weeks compared to standard mitoxantrone-prednisone chemotherapy. Superior overall survival was also observed with docetaxel given every 3 weeks, and although the median survival increment was a modest 2.4 months, the hazard ratio of 0.76 indicated a 24% reduction in the risk of death for these patients over the course of this trial. Petrylak et al[2] compared docetaxel-estramustine with mitoxantrone-prednisone in 674 eligible men with HRPC, and reported similar results including an overall survival hazard ratio of 0.80 associated with the taxane-based regimen. Tannock et al reported less frequent and severe cardiovascular and gastrointestinal toxicities, and this regimen of docetaxel-prednisone given without estramustine has become the standard regimen for treatment of men with HRPC. It is unusual to observe survival benefits with single agent chemotherapy, suggesting that docetaxel may have a relatively unique and potent effect on prostate cancer cells.

Biological rationale

A large body of basic scientific data is converging with an emphasis on changes in the molecular biology of the androgen receptor after ADT leading to the development of androgen independence and resistance. Using microarray-based profiling of prostate cancer xenograft models, Chen et al[6] reported that a modest increase in androgen receptor nRNA and protein was the only change consistently associated with the development of androgen resistance, and was necessary and sufficient to convert prostate cancer growth form hormone-sensitive to hormone-refractory. Upregulation of antiapoptotic and cell survival proteins such as bcl-2 and clusterin has also been identified as important in the genesis of HRPC.[7] As androgens exert antiapoptic effects in prostate cancer cells, it would be expected that anticancer therapies such as radiotherapy and chemotherapy would be less effective in the presence of physiological levels of androgens. However, until recently a preclinical basis for the optimal sequencing of chemotherapy drugs with ADT has been lacking. Eigl et al[8] studied the sequencing of chemotherapy and castration in two androgen dependent prostate cancer xenograft models. Each group of xenografted mice was divided into three groups: immediate castration followed by paclitaxel at tumor progression, immediate paclitaxel followed by castration at tumor progression, and immediate combined castration plus paclitaxel. Results with both xenograft models were similar, and showed optimal tumor regression and superior survival with immediate combined treatment. The worst tumor control was with immediate chemotherapy alone followed by castration, and upregulation of genes associated with androgen resistance was identified in these mice. These data not only provide preclinical evidence for simultaneous rather than sequential initiation of ADT and chemotherapy, but also provide further support for study of chemohormonal therapy in non-HRPC.

Clinical rationale

Despite a lack of convincing evidence for the efficacy of chemotherapy in prostate cancer until the past decade, a number of RCTs studying the addition of chemotherapy to ADT in men with advanced

hormone-naïve prostate cancer have been completed and reported.[9] Of 21 RCTs reporting overall survival results, none reported benefits of adding cytotoxic drugs to ADT. However, most of these trials were insufficiently powered to detect modest but potentially clinically significant benefits. As well, none studied taxane drugs such as docetaxel, and only two trials studied other chemotherapy drugs known to have efficacy in HRPC (epirubicin, mitoxantrone). These two RCTs are of interest, as they appear to provide further rationale for studying chemohormonal therapy in non-HRPC. Pummer et al[10] reported 117 men with untreated stage D prostate cancer who were treated with bilateral orchiectomy plus flutamide and randomized to no chemotherapy or epirubicin 25 mg/m^2 iv weekly for 12 doses. Progression-free survival was superior in the group receiving chemotherapy (median 18 versus 12 months, P<0.02). Overall survival was a median 8 months longer in the chemotherapy group (30 versus 22 months, p=0.12), but the trial was underpowered to statistically prove this difference. Quality Time Without Symptoms and Toxicity (QTWiST) analysis also favored the chemotherapy arm (7.2 months, p<0.05). Wang et al[11] reported 96 patients with untreated locally advanced or metastatic prostate cancer treated with leuprolide plus flutamide and randomized to either no chemotherapy or mitoxantrone 12 mg/m^2 iv every 3 weeks for four doses. Overall survival was longer in the chemotherapy group (median 27 versus 24 months, p=0.09) but was not statistically proven. The difference appeared to be mainly due to a difference in the survival of patients with locally advanced disease (80 versus 36 months, p=0.04).

A number of single arm trials have studied chemotherapy sequenced with local therapy either alone or in combination with ADT. One of the largest of these was completed by the Canadian Urological Oncology Group, who treated 72 men with high-risk localized prostate cancer with neoadjuvant buserelin depot with weekly docetaxel for 6 months prior to radical prostatectomy.[12] Toxicity was generally mild. Two patients had pathological complete response with no histological evidence of prostate cancer in their prostatectomy specimen, a phenomenon not observed with ADT alone. An additional 12 patients had only microfoci of prostate cancer in their prostatectomy specimens. Although conclusions are limited by the lack of a comparator group, these observations support additional anticancer effects of docetaxel in a subgroup of high-risk localized prostate cancer patients. The rapid accrual to this study also supports the feasibility of studying this approach further in large scale RCTs.

Although these data provide supportive clinical rationale for chemohormonal therapy in non-HRPC, other clinical factors need to be considered in the design of RCTs. Risk identification is important in prostate cancer, as more intensive systemic therapy may increase acute morbidity and even mortality, and the benefits of chemotherapy on survival are usually modest. Currently available prognostic factors do not precisely identify those men with localized prostate cancer who will die of it, and in older patients the risk of death from competing risks often exceeds that from prostate cancer. Biochemical failure after local therapy is often a stimulus for ADT, but is not a particularly good surrogate for death from prostate cancer. Better clinicopathological information such as individual PSA dynamics before and after local therapy may help; however, a better understanding of prostate cancer biology via molecular medicine is needed.

Current and planned RCTs

Building on the results of the CUOG neoadjuvant trial, the CALGB 90203 trial randomizes men with high-risk localized prostate cancer to 4 months of leuprolide with or without six doses of 3 weekly docetaxel prior to radical prostatectomy. The primary endpoint is biochemical failure-free rate at 5 years. In the SWOG S9921 adjuvant trial, men identified with high-risk features post-prostatectomy are randomized to ADT alone or in combination with 3 weekly mitoxantrone for six doses. The primary endpoint is overall survival and 1360 men will be randomized. Trial 3501 will randomize 2172 men to either immediate adjuvant therapy or treatment deferred until the time of biochemical recurrence. Treatment in both arms consists of goserelin for 18 months with randomization to no chemotherapy or six doses of 3 weekly docetaxel.

Chemohormonal therapy is also being tested in men with biochemical recurrence following local therapy and men with hormone naïve metastatic disease. A trial led by the Memorial Sloan Kettering Cancer Center will randomize men with biochemical recurrence after local therapy and PSA doubling times of $\leq$ 9 months to leuprolide for 2 years with or without eight doses of 3 weekly docetaxel. The MRC STAMPEDE trial will enroll men with either high-risk localized disease, biochemical recurrence after local therapy, or metastatic disease to treatment arms combining ADT with or without docetaxel,

zoledronate, or a combination of both. This trial will expand internationally once the optimal treatment arms have been identified.

Conclusions

There is considerable intuitive, preclinical, and clinical rationale supporting the potential benefit of chemotherapy in addition to ADT in sequence with local therapies in selected patients with high-risk localized prostate cancer, as well as in men with biochemically recurrent prostate cancer after local therapy, and in men with hormone-naïve metastatic disease. Large scale RCTs investigating this hypothesis are currently underway or about to be initiated, and a number of these trials will be available in Canada. In addition to its role in palliation and disease control in HRPC, chemotherapy may soon have a role earlier in the natural history of prostate cancer. □

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