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Chemotherapy for oligometastatic prostate cancer

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Abstract

Purpose of review—To analyze recent trials of upfront chemotherapy to determine how this paradigm can be applied to oligometastatic prostate cancer patients.

Recent findings—Upfront chemotherapy prolongs survival in metastatic prostate cancer, according to the ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer and STAMPEDE docetaxel trials. However, the benefit is driven by the high volume subset and may not apply low-volume/oligometastatic patients.

Summary—Oligometastatic patients may not all share the same biology. Advanced imaging techniques may help to more accurately identify truly oligometastatic patients. Molecular markers will be necessary to distinguish oligometastatic patients who fare well enough with androgen deprivation therapy alone as opposed to those for whom upfront chemotherapy may be beneficial. Emerging molecular markers of docetaxel sensitivity, such as loss of lysine-specific demethylase 5d, warrant prospective validation with one goal of identifying oligometastatic patients with greatest likelihood of benefit from this strategy.

Keywords

chemotherapy; oligometastatic prostate cancer; predictive biomarkers

INTRODUCTION

Oligometastatic (‘oligo’ = few) in the prostate cancer literature has been used to describe patients with three or fewer visible lesions [1], whereas others refer to five or fewer. Others may refer to this as ‘low-volume’ metastatic disease. The St Gallen consensus definition is three or fewer metastases in bone and/or lymph node (LN) only [2]. The intention of such characterizations has often been to identify patients with a different biology, with an indolent course or longer natural history with androgen deprivation therapy (ADT) alone and for whom long-term remissions might be possible with the addition of ablative (surgery or radiation) therapy to the primary organ and/or potentially to the limited metastatic sites.

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Conflicts of interest

There are no conflicts of interest.

However, an alternative clinical application of this classification could be to identify patients for whom standard therapy with ADT alone and sequential therapy with castration-resistant prostate cancer (CRPC) life prolonging agents achieves satisfactory control compared with those with higher volume disease. Ultimately molecular predictors are needed to categorize oligometastatic patients as more likely to benefit from chemotherapy or less likely to have durable control with standard ADT. In the current landscape, without molecular classifiers, we will review what is known about the biology of oligometastatic prostate cancer and considerations in selecting some of these patients for intensified first line therapy, incorporating emerging literature on treatment with early chemotherapy.

ADT utilizing luteinizing hormone release hormone agonist or antagonist medication, sometimes in combination with androgen receptor (AR) inhibition, remains the cornerstone of systemic therapy for advanced prostate cancer. Although ADT can result in prolonged survival for metastatic prostate cancer patients, it is not thought of as being capable of eradicating established metastatic disease that is evident on standard imaging, because of the almost inevitable development of resistance. Looking at outcomes with ADT across the spectrum of disease states, a hypothesis emerges that with larger volume of disease there is increased likelihood of inherent 'de novo' resistance. For example, in the adjuvant setting a course of ADT appears to increase cure [3,4]. In biochemically recurrent disease, median time to castration resistance is approximately 2.5 years [5], whereas in metastatic patients median time to castration resistance is 1–1.5 years [6]. In Southwest Oncology Group (SWOG) 9916, which compared intermittent versus continuous ADT in patients with metastatic hormone-sensitive prostate cancer, not only was median overall survival (OS) longer in the low-volume patients, but continuous ADT had a stronger survival benefit [7]. Trials reporting outcomes based on volume of disease are summarized in Table 1. Overall, defining oligometastatic disease with more precision may, to some extent, define patients for whom ADT is a more effective tool and for whom it is inadequate treatment. However, to date increased cure with adjuvant hormonal therapy has only been shown for localized disease and with salvage radiation.

PROBLEM 1: DEFINING OLIGOMETASTATIC

A numerical definition of low volume clearly miscategorizes some patients with rapidly progressing or higher volume disease, by including a patient whose 'snapshot' in time reveals three to four or fewer lesions but who really harbors many additional metastatic deposits, too small yet to be visible radiographically but which will appear a few months later. The evolution of molecular imaging with greater sensitivity will likely shift patients from 'biochemical recurrence' on conventional imaging to 'oligometastatic' on more sensitive imaging by detecting disease which is still occult to computed tomography and technetium bone scans. For instance, Sodium Fluoride F18 PET bone scans have been shown to be more sensitive and specific than conventional technetium bone scans at identifying metastatic disease [10]. F18 fluciclovine PET scanning, which was approved by Federal Drug Administration for imaging men with biochemically recurrent prostate cancer, can detect extraprostatic disease, including bone metastases, with sensitivity of 84.2% and specificity of 89.7%, even with low prostate specific antigen (PSA) values (<1 ng/dl) [11]. With this increased sensitivity to detect metastases, the proportion of patients with

oligometastatic disease based on any definition will shift. Accurate definition of volume of metastatic disease may increase the relevance of the oligometastatic definition as it may better inform treatment decision-making.

Emerging data from trials of adding local ablative therapy to oligometastatic deposits (as well as treating the primary) are not universally successful in eradicating all disease, confirming that current imaging is not yet able to definitively exclude disease outside what is visible [12]. This suggests systemic therapy will still play an important role. In one experience, stereotactic radiotherapy was applied to oligometastases (three or fewer total lesions in bone, LN, or visceral) in patients who had relapsed after definitive local therapy. In this study 30–50 Gy was applied without ADT to a total of 70 lesions in 50 patients; at a median follow-up of 2 years only 18 patients remained disease free. Notably, all relapses occurred outside of the irradiated areas [13], indicating that occult metastases existed. This argues for systemic therapy as an important component even in oligometastatic disease. This is not too dissimilar to the finding that 2 years of bicalutamide decreased recurrence and improved OS in patients treated with salvage radiation post radical prostatectomy [14■].

PROBLEM 2: IDENTIFYING PATIENTS WITH MORE ANDROGEN RECEPTOR-DEPENDENT DISEASE VERSUS THOSE WITH MORE RAPID EVOLUTION TO CASTRATION-RESISTANT EVEN WITHIN OLIGOMETASTATIC PATIENTS

The behavior of metastatic prostate cancer varies widely, with a small fraction of patients progressing early on and rapidly, regardless of number or distribution of metastases. Because there are multiple mechanisms by which prostate cancer cells become castration resistant, there is currently not any single molecular marker that can be used to identify these cells to identify when they appear. The traditional treatment paradigm of intensifying therapy after the emergence of CRPC assumes that castration drives emergence. However, if resistant clones exist before application of castration therapy, or if a patient's cancer cells have some inherent ability to become resistant earlier into treatment, then early introduction of intensified therapy could yield a deeper remission and better OS. Without technology to identify the presence of resistant cells, we cannot determine whether de novo resistance indeed exists, or drives behavior, much less whether this explains the success of the upfront intensification approach.

PSA nadir at 7 months into first-line ADT is one strongly prognostic clinical feature; in a combined analysis of two SWOG trials (S9916 in metastatic CRPC and S9346 in metastatic hormone-sensitive prostate cancer) it was noted that patients who failed to achieve a PSA nadir below 4ng/dl had median survival of 16 months compared with 69 months for those whose PSA did nadir [15]. But how do we detect those patients who are likely to fail to nadir prior to initiating treatment? If it were possible, would intensification in this select population yield similar results to universal upfront application? The SWOG trial S1014 (NCT01309672) will contribute some information toward answering that question; in this trial men whose PSA failed to nadir below 4 ng/dl at 7 months into first-line ADT for metastatic prostate cancer were treated with abiraterone immediately, rather than waiting

for castration resistance. The outcomes in this trial, compared to the Hussain *et al.* [15] data set, may yield some information about moderately early intensification of therapy. Patients who fall on the other side of the bell curve, remaining sensitive to standard first-line ADT for many years, conceivably may benefit less from upfront intensification of therapy, especially with an agent such as docetaxel with its substantial associated treatment burden. Understanding the biology and identifying molecular predictors of early progressors and long-term responders remains a high priority.

PROBLEM 3: PREDICTORS FOR CHEMOTHERAPY EFFICACY IN PROSTATE CANCER ARE LACKING

Docetaxel is a chemotherapy agent which works by stabilizing microtubules, thus as with other chemotherapy agents it may be expected to be most effective in the setting of rapidly doubling cancer cells. However, another mechanism of action specific to prostate cancer has been elucidated: blockade of AR transport to the nucleus [16] and blockade of nuclear transport of AR, manifest as accumulation in the cytoplasm, is associated with response [17]. Docetaxel chemotherapy became the standard of care for metastatic CRPC after two trials were published simultaneously in the *New England Journal of Medicine* in 2004, the SWOG 9916 trial comparing docetaxel and estramustine versus mitoxantrone [18] and the TAX327 study, comparing docetaxel every 3 weeks or weekly versus mitoxantrone [19] establishing a survival benefit for docetaxel. These studies reported baseline characteristics including visceral metastases, but did not identify the proportion of patients who had low-volume or oligometastatic disease. Measuring AR accumulation in circulating tumor cells may provide an assay for docetaxel efficacy early into treatment, but still would not achieve the aim of identifying sensitive or resistant patients and is not yet available as a standardized, validated, commercial assay.

More recently, studies have asked the question of whether using docetaxel early would have bigger impact. In fact, adding docetaxel chemotherapy upfront with first-line ADT has now been proven to significantly improve survival in prostate cancer in the ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) [20■■■] and STAMPEDE [21■■■] studies, although the smaller Groupe d'étude des tumeurs urogénitales (GETUG) study did not find a benefit [22■], summarized in Table 2. However, the survival advantage thus far appears to be driven by the 'high-volume' disease group, (those with four or more bone metastases with one outside the axial skeleton or visceral metastases), according to the long-term follow-up CHAARTED and supported by the trend in favor of docetaxel in high volume in the GETUG15 study. Subset analysis of survival benefit based on high volume versus low-volume disease status has not yet been performed in the STAMPEDE docetaxel trial. Notably, the STAMPEDE docetaxel study did include men with nonmetastatic (M0) disease, and no survival advantage at the early was evident in this group: hazard ratio 0.95 (95% confidence interval, 0.62–1.47) compared with 0.76 (95% confidence interval, 0.62–0.92) for metastatic patients. It is worth noting that the M0 population included a heterogeneous population: patients who have localized high-risk disease and treated with ADT and radiation or ADT alone, and also patients with biochemical recurrence receiving ADT. There is a prolongation in time to PSA

rise with early docetaxel and longer follow-up will better determine whether this translates into a metastasis free and OS benefit for one or more other subpopulations in the M0 group. The Radiation Therapy Oncology Group 0521 and GETUG 12 trials have also reported on the results of ADT and radiation \pm docetaxel with some evidence of benefit of the addition of docetaxel. Hopefully, a more crisply defined metastasis-free survival and OS benefit can be defined for docetaxel in patients with high risk localized patients treated with long-course ADT and radiation treated with curative intent.

One reason for the lack of a clear impact of upfront chemotherapy in patients with oligometastatic/low-volume disease could be that the imaging gives us a 'snapshot' in time, including patients who truly have limited distribution of metastases as well as those with many more sites of occult disease which would become apparent if repeat images were taken a few months later. Thus patients who appear to be oligometastatic on conventional imaging likely include not only patients with indolent biology, but patients with aggressive biology. Furthermore, patients meeting the oligometastatic definition on imaging include those whose primary prostate cancer had previously been treated with local therapy as well as patients who present already with metastatic disease, two populations with distinct cancer behavior. Patients whose prostate cancer recurs after definitive management of the primary experience longer cancer control with ADT [24,25]. Unfortunately, standard clinical risk stratification parameters such as Gleason score, may not help select which oligometastatic patients would benefit from upfront chemotherapy. In the STAMPEDE and CHAARTED trials, Gleason score 9–10 did not seem to predict benefit from upfront chemotherapy in, despite the fact that it has sometimes shown an association with shorted duration of cancer control with ADT [26]. In the CHAARTED trial, when Gleason and volume of metastatic disease was included in the multivariate analysis, Gleason was no longer significant and probably related to the fact most patients who present with de novo metastatic disease have high-volume metastatic disease and have high-grade disease in their prostate [27].

Just as there may be more specific biological markers (AR variants, p53, phosphatase and tensin homolog, retinoblastoma status), there may also be some histological subtypes of prostate cancer for which chemotherapy may be indicated even in the oligometastatic state. These may include ductal and neuroendocrine/small cell variants. Ductal prostate cancer is associated with lower serum PSA levels, which may be a marker of less AR-driven disease, and with increased prostate cancer mortality even in the nonmetastatic setting [28]. For these patients, chemotherapy may be considered in oligometastatic setting. Neuroendocrine differentiation may also be an indication for chemotherapy, even for patients with oligometastatic disease burden. These are questions that should be evaluated prospectively, just as is planned for new biological markers.

Molecular understanding of docetaxel sensitivity is finally evolving. For example lysine-specific demethylase 5d (KDM5D) functions as a tumor suppressor gene via transcriptional control of genes associated with invasion, such as matrix metalloproteinases[29]. KDM5D is also involved with transcriptional activation of AR targets, and its absence has been associated with docetaxel resistance in in-vitro models [30■■■]. Further elucidation of molecular underpinnings of docetaxel sensitivity and resistance will be critical to optimally selecting which patients with oligometastatic disease benefit from upfront chemotherapy.

Biological or histological markers that can identify patients with oligometastatic disease who benefit from upfront ADT and docetaxel could then be studied in even earlier, more ‘micro’ metastatic settings such as adjuvant to definitive local therapy. Namely, if ADT and radiation and docetaxel is found to be clearly beneficial/increase cure rate more than ADT and radiation in high-risk localized disease by greater eradication of micrometastatic disease, it may also have a role in oligometastatic disease when added to local ablative therapy to all disease seen on conventional scans and ADT. However, we would have to show ADT and radiation in this setting is more effective than ADT alone or local ablative therapy alone in oligometastatic disease first.

CONCLUSION

There is a paucity of compelling data showing a benefit for chemotherapy in oligometastatic prostate cancer, and any benefit may be outweighed by the treatment burden with docetaxel, it could be argued that the default is not to offer chemotherapy, unless a specific indication exists for an individual patient. Although there are no clearly defined guidelines on how to identify such patients, rapid disease growth and ductal or neuroendocrine histology might be reasonable current clinical selection factors. Molecular predictors are in development which will facilitate rational selection between chemotherapy and abiraterone in the first-line metastatic setting. With the publication of two randomized studies (LATITUDE and STAMPEDE-abi) identifying a survival advantage for upfront abiraterone added to the CHARTED data set, abiraterone represents a better choice for most oligometastatic patients based on a lower treatment burden. However, it is beyond the scope of this article to review in detail the observation that there were very few patients accrued with low-volume disease to LATITUDE and STAMPEDE abiraterone to also address the question whether sequential therapy is as effective as upfront combination therapy with abiraterone in the oligometastatic patient population

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KEY POINTS

- The current evidence does not support use of chemotherapy upfront for oligometastatic prostate cancer.
- There are likely oligometastatic prostate cancer patients who will benefit from chemotherapy but molecular predictive markers need to be validated as clinical characteristics are not specific enough to identify these patients prior to initiating treatment.
- Advances in imaging will impact proportions of patients meeting the oligometastatic definition.

Randomized trials which have reported outcomes differentially based on volume of disease (i.e., oligometastatic or low-volume versus high volume)

Table 1.

| Trial (author) | Treatment arms | Definition of oligometastatic or low volume | Patients meeting low volume definition (N/total) | Outcome interaction with metastatic burden |
|--|---|--|--|---|
| SWOG 9916 (Hussain <i>et al.</i>) [7] | Intermittent ADT Continuous ADT (mHSPC) | Confined to vertebral, and/or pelvic bones, and/or LNs | 792/1535 | OS better with continuous ADT (HR 1.19; 95% CI, 0.98–1.43) for low and high volume |
| CHAAARTED (Sweeney <i>et al.</i>) [8] | ADT standard ADT and docetaxel (mHSPC) | Fewer than four bone metastases, none outside axial skeleton | 277/790 | OS benefit for upfront docetaxel not significant (HR 1.04, 95% CI, 0.7–1.55) for low volume |
| ALSYMPCA (Parker <i>et al.</i>) [9] | Standard care ^a Standard and radium223 (mCRPC) | Less than six bone metastases (visceral excluded entirely) | 138/921 | OS benefit weaker than higher volume subsets (HR for OS 0.95, 95% CI, 0.46–1.95) |

ADT, androgen deprivation therapy; ALSYMPCA, apfrenadin in symptomatic prostate cancer patients; CHAAARTED, ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; CI, confidence interval; HR, hazard ratio; LN, lymph node; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; SWOG, Southwest Oncology Group.

^aStandard care for mCRPC included bicalutamide, ketoconazole, estrogen, and bisphosphonates.

Characteristics of patients studied (i.e., low-volume and high-volume disease) and key outcomes for upfront docetaxel in metastatic prostate cancer in three randomized trials

Table 2.

| | CHAARTED <i>n</i> =397 docetaxel patients | STAMPEDE <i>N</i> =1066 docetaxel patients ^a | GETUG <i>N</i> =189 docetaxel patients |
|------------------------------|--|--|---|
| Median age (range) | 64 (36–91) | 65–66 ^a (60–70) | 63 (57–68) |
| #/% Low volume | 134 | Unknown | 100 |
| #/% High volume | 263 | Unknown | 92 |
| # (%) lung metastases | NR | 6 | 44 (11%) |
| # (%) liver metastases | NR | 13 | 12/395 |
| HR overall survival (95% CI) | 0.61 (0.47–0.8) | 0.76 (0.62–0.93) | 0.9 (0.69–1.81) |
| HR low volume | 1.04 (0.7–1.55) | Unknown | 1.02 (0.67–1.55) |
| HR high volume | 0.63 (0.5–0.79) | | 0.78 (0.56–1.09) |
| Any grade 3–4 toxicity | 29.3% | 52% | NR |
| Grade 3–4 neutropenia | 12% | 10.8% | 41% ^b |
| Grade 5 toxicity | 1 (0.3%) | 8 (1.2%) | 4 (2.1%) |

CHAARTED, ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; CI, confidence interval; HR, hazard ratio; GETUG, Groupe d'Etude des Tumeurs Urogénitales; NR, not reported.

^aIncludes 550 standard of care (SOC) and docetaxel and 516 SOC and zoledronate and docetaxel.

^bThe rate of grade 3/4 neutropenia decreased to 15% after an amendment to use prophylactic GCSF.

Adapted with permission [20,21,23].