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The role of hormone therapy and chemotherapy in oligometastatic prostate cancer

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ABSTRACT

Oligometastatic disease was proposed by Hellman and Weichselbaum in 1995 as an intermediate tumour state between localised lesions and widespread metastases, characterised by the limited number and size of metastases in specific organs such as lung, liver, bone or even brain. The oligometastatic state has increasingly been recognised as a unique clinical state during which local ablative treatment can be effective in several types of cancer, including prostate cancer. However, the role of systemic therapy, such as hormone therapy and chemotherapy, is not yet well known. Some promising data for local ablative therapy have emerged, but it remains unclear whether local therapy can eliminate the need for, androgen-deprivation therapy (ADT), or reduce the required duration. In addition, several randomised phase III trials have demonstrated survival benefits from the addition of docetaxel or abiraterone to ADT in patients with metastatic hormone-sensitive prostate cancer. These findings suggest that such aggressive treatments may improve clinical outcomes for patients with oligometastatic prostate cancer. However, the efficacy of these treatments may depend on the volume of metastases, with higher efficacy for high-volume disease. Therefore, further investigation including stratification by disease volume is warranted. This review will discuss the current evidence and controversies surrounding the role of systemic therapy in patients with oligometastatic prostate cancer.

INTRODUCTION

Oligometastatic disease was proposed by Hellman and Weichselbaum in 1995 as an intermediate tumour state between localised lesions and widespread metastases, characterised by the limited number and size of metastases in specific organs such as lung, liver, bone or even brain.[1] The oligometastatic state is defined as a limited number of metastases. Cut-offs of a maximum of three or five lesions are used in the literatures.[2 3] Yet, there is no definite consensus regarding the number or the location of these metastases.[4] In several types of cancer, such as colorectal,[5] lung[6] and prostate cancer,[2] it has been reported that selected patients with oligometastasis have good prognosis when treated with metastasis-directed treatment.

The role of systemic therapy, such as hormone therapy or chemotherapy, in the treatment of patients with oligometastatic prostate cancer remains to be elucidated. Generally, the existence of metastases is considered evidence of systemic spread, and thus systemic therapy should be indicated for patients with metastatic cancer. However, the use of a multimodal approach that includes local ablative therapy, with or without short-term androgen deprivation therapy (ADT) to avoid toxicity and quality-of-life deterioration that can result from long-term ADT, is worthy of consideration. This is based on several sources of evidence indicating that patients with prostate cancer with a limited number of metastases have a better prognosis under such multimodal approaches.[2 7–12] However, these literatures including heterogeneous population because of the lack of definite criteria for oligometastasis. The cut-off number of metastasis is used less than three or five. The site of metastasis includes bone, lymph node, visceral or both. The timing of developing metastasis is synchronous or metachronous.

By contrast, using more aggressive treatment strategy can have considerable benefits. There is evidence showing that the addition of docetaxel or abiraterone to ADT in metastatic hormone-sensitive prostate cancer can prolong overall survival (OS).[13–16] These considerations raise the following three clinical questions regarding treatment strategies for patients with oligometastatic prostate cancer, and this review will discuss the current evidence and controversies surrounding them:

1. Is ADT necessary for oligometastatic hormone-sensitive prostate cancer?
2. Is the addition of docetaxel to hormone therapy recommended for patients with oligometastatic hormone-sensitive prostate cancer?
3. Is the addition of abiraterone acetate plus low-dose prednisone/prednisolone to

ADT recommended for oligometastatic hormone-sensitive prostate cancer?

LITERATURE SEARCH

We carried out a systemic literature search by PubMed up to 31 December 2018 using following search keywords: (oligometastatic [Title/Abstract] OR oligometastasis [Title/Abstract] OR oligometastases [Title/Abstract]) AND ('prostate cancer' [Title/Abstract]). We restricted publication language to English. The initial search yielded 194 articles. In all, 114 articles of them were excluded as they were review, systematic review, letter, comments, editorial, clinical trial design or case reports of publication type. We performed full review for the remaining 80 articles. Of these, seven articles were excluded because they were not related to oligometastasis. In the remaining 73 articles, one prospective randomised clinical trial[17] and three prospective single-arm clinical trials[18–20] were included.

CLINICAL QUESTIONS

1. Is ADT necessary for oligometastatic hormone-sensitive prostate cancer?

Our literature review revealed that no prospective randomised data are available to show whether ADT is necessary or not in patients with oligometastatic hormone-sensitive prostate cancer. ADT remains the recommended treatment for patients with metastatic hormone-sensitive prostate cancer, according to some guidelines.[21 22] However, these guidelines do not stratify recommended treatments according to the volume of metastatic disease, such as oligometastatic, high-volume or low-volume disease groups. As a result, ADT is presently recommended for the general population of patients with metastatic prostate cancer regardless of metastasis volume. In the European Association of Urology guidelines, treatment recommendations for asymptomatic metastatic prostate cancer are distinct from symptomatic disease due to the lack of high-quality evidence for survival benefits resulting from immediate ADT for patients with asymptomatic prostate cancer.[21] The guidelines make two recommendations based on status: for *Grade A* status, it is recommended that asymptomatic M1 patients be offered immediate castration to defer progression to a symptomatic stage and prevent serious disease progression–related complications; for *Grade B* status, discussion of deferred castration with well-informed patients is recommended, as this lowers the treatment side effects.[21] Based on the concept of avoiding adverse events and quality-of-life implications resulting from long-term ADT treatment,[21] a clinical question has been established regarding whether ADT should be deferred or eliminated when metastasis-directed therapy (MDT) is initiated, especially in oligometastatic disease.

Several retrospective and single-arm studies have suggested that MDT may delay clinical progression. One systematic review, including 15 single-arm case series studies (12 retrospective and 3 prospective studies) consisting of a total of 450 patients with oligometastatic prostate cancer suggested that MDT had promising efficacy. The review showed that 51% of patients were progression-free at 1–3 years after salvage MDT.[23] However, the site of metastases, type of MDT and concurrent treatment varied, and 61% of patients received adjuvant ADT after MDT in this systematic review.[23]

A multi-institutional retrospective analysis was conducted, consisting of 119 patients with recurrent oligometastatic prostate cancer who received stereotactic body radiotherapy (SBRT).[2] A temporary course (less than 12 months) of adjuvant ADT concurrent with SBRT was prescribed for 50% of patients. The median distant metastatic progression-free survival from SBRT was shorter than that for SBRT plus adjuvant ADT at 18 months (95% CI, 17.1 to 18.8 months) versus 25 months (95% CI, 18.3 to 31.6 months), although this difference was not statistically significant (p=0.09).[2]

In terms of prospective clinical trials, there are one randomised phase II trial[17] and three single-arm phase II trials[18–20] that evaluated the efficacy and toxicity of MDT. The Surveillance or Metastasis-directed Therapy for Oligometastatic Prostate Cancer Recurrence Trial was performed to assess the benefits of MDT (mainly SBRT) for all detectable metastatic lesions compared with surveillance in patients with asymptomatic hormone-sensitive prostate cancer with three or fewer extracranial recurrent metastatic lesions.[17] In total, 62 patients were enrolled, of these, 58% of patients had only nodal metastasis. The median ADT-free survival, which was the primary endpoint of the trial, was 13 months (80% CI, 12 to 17 months) in the surveillance group, and 21 months (80% CI, 14 to 29 months) in the MDT group (HR, 0.60; 80% CI, 0.40 to 0.90; log rank p=0.11), although 50% of patients in the MDT arm received a temporary course of adjuvant ADT concurrent with SBRT.[17] Of three single-arm phase II trials, one had published only preliminary toxicity data,[18] and one trial was eligible for de novo oligometastatic prostate cancer and all patients received ADT as initial therapy.[20] In the remaining one trial,[19] 30 patients with recurrent oligometastatic prostate cancer were enrolled and received SBRT against all visible metastatic sites. Of these, 6 (18%) patients were castration resistant and 12 (36%) patients had only nodal metastasis. The local progression-free survival and the distant progression-free survival at 2 year was 93% (95% CI, 84% to 100%) and 39% (95% CI, 25 to 60), respectively. The ADT-free survival at 2 years in 22 patients who did not receive ADT at the time of SBRT was 48% (95% CI, 31% to 75%). However, the number, location (nodal or bone) and timing (synchronous or metachronous) of metastasis should be considerable in the interpretation of these trials because these factors would have impact on OS.[24] Additionally, ADT-free survival was not well defined or validated endpoint and their clinical importance was still unclear. Prospective randomised phase III trial evaluating OS as primary endpoint is required.

Interestingly, the Advanced Prostate Cancer Consensus Conference (APCCC 2017), despite being held before the publication of these prospective trials, found that only 8% and 12% of panellists voted for local ablative treatment (radiotherapy or surgery) of all lesions without ADT for patients with synchronous and metachronous oligometastatic hormone-sensitive prostate cancer, respectively.[4]

Taken together, ADT remains the standard of care for patients with oligometastatic hormone-sensitive prostate cancer, and MDT may be a potentially promising treatment option to replace or differ life-long ADT for selected patients with oligometastatic prostate cancer. Further investigation is warranted to assess the role of MDT in standard therapy.

2. Is the addition of docetaxel to hormone therapy recommended for patients with oligometastatic hormone-sensitive prostate cancer?

Our literature review revealed that no prospective randomised data are available to show whether docetaxel adding to hormone therapy is more effective than hormone therapy alone in patients with oligometastatic hormone-sensitive prostate cancer. However, unless objectives are limited in patients with oligometastasis, three randomised phase III trials: GETUG-AFU 15,[25] CHAARTED-E3805,[13] and the STAMPEDE trial[14] have evaluated the efficacy of docetaxel in addition to ADT compared with ADT alone in patients with hormone-sensitive prostate cancer. All enrolled patients in the GETUG-AFU 15 and CHAARTED-E3805 trials had metastases. By contrast, the STAMPEDE trial has a multi-arm, multistage platform design that included heterogeneous patients, such as de novo M0 and M1 patients, and M0 or M1 patients who were previously locally treated. The information regarding the volume of metastatic disease was available for the GETUG-AFU 15 and CHAARTED-E3805 trials, but not for the STAMPEDE trial.[26] In the CHAARTED-E3805 trial, high-volume disease was defined by the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis; patients without these conditions were classified as low-volume disease, and around 30% of patents with low-volume disease were enrolled (33.8%, 134 out of 397 patients and 36.4%, 143 out of 393 patients in the ADT plus docetaxel and ADT alone groups, respectively).[13] In comparison, post hoc analysis in the GETUG-AFU15 trial reveals that almost half of the patients were classified as having low-volume disease defined by CHARTED-E3805 criteria (52%, 100 out of 192 patients and 53%, 102 out of 193 patients in the ADT plus docetaxel and ADT alone groups, respectively).[27] According to the definition of the volume of disease, patients with low-volume disease is classified as oligometastatic status. Among high-volume disease, the patients with solitary visceral metastasis can be classified as oligometastatic status; however, it is expected that the incidence of such patients is extremely rare. As a result, we use the data of low-volume disease as a substitute for the one of oligometastatic disease.

In the CHAARTED trial, docetaxel in addition to ADT compared with ADT alone resulted in prolonged OS for patients with metastatic hormone-sensitive prostate cancer in the overall population (HR for death with ADT plus docetaxel=0.61; 95% CI, 0.47 to 0.80; p<0.001).[13] Although subgroup analysis stratified with high- and low-volume disease is under powered to evaluate OS, among patients with high-volume disease, median OS in the ADT plus docetaxel group versus ADT alone group was 49.2 and 32.2 months, respectively (HR for death with ADT plus docetaxel=0.61; 95% CI, 0.45 to 0.81; p<0.001).[13] In contrast, among patients with low-volume disease, although they comprised only 35% of the patients included in this study, the addition of docetaxel to ADT had no significant effect on OS prolongation (HR for death=0.60; 95% CI, 0.32 to 1.13; p=0.11).[13] This trend was confirmed by long-term survival analysis in this study and was repeated in both subgroups of patients: those with de novo metastases and those with prior local therapy, although this subgroup analysis was not prespecified.[28]

In the GETUG-AFU 15 trial, no OS benefit was discerned in either the overall trial population (HR for death with ADT plus docetaxel=0.88; 95% CI, 0.68 to 1.14; p=0.3), those with high-volume disease (HR for death with ADT plus docetaxel=0.78; 95% CI, 0.56 to 1.09; p=0.1), or those with low-volume disease (HR for death with ADT plus docetaxel=1.02; 95% CI, 0.67 to 1.55; p=0.9).[27]

Based on the subgroup data available for the CHAARTED and GETUG-AFU 15 trials, a meta-analysis of treatment efficacy according to disease volume (high vs low volume) defined by CHARTED-E3805 criteria was performed. The HR for the addition of docetaxel to ADT for OS was 0.67 (95% CI, 0.51 to 0.88) in high-volume disease and 0.80 (95% CI, 0.49 to 1.32) in low-volume disease.[26] The meta-analysis did not show a significant interaction between disease volume and drug efficacy, likely due to limited statistical power.[26]

Interestingly, oligometastatic prostate cancer was added as one of the most important controversial areas for discussion related to the management of men with advanced prostate cancer at the APCCC 2017.[4] Sixty-one per cent of panellists voted for local treatment plus ADT for patients with de novo oligometastatic prostate cancer. Of these, 33% of panellists did not consider that the addition of docetaxel to ADT was required, and 39% of panellists agreed with docetaxel addition only for a minority of selected patients.[4]

Taken together, we cannot conclude whether the addition of docetaxel to ADT is effective in patients with oligometastatic hormone-sensitive prostate cancer because the data based on disease volume in this subgroup analysis had limited statistical power. Moreover, the overall trial population data demonstrated the clinical efficacy of chemohormone therapy for improving OS. However, the disease volume in patients with oligometastasis may be much lower, and their prognosis with ADT treatment alone may be better than patients classified with low-volume disease.

Therefore, we should be careful when selecting patients for treatment with docetaxel in addition to ADT.

3. Is the addition of abiraterone acetate plus low-dose prednisone/prednisolone to ADT recommended for oligometastatic hormone-sensitive prostate cancer?

Our literature review revealed that no prospective randomised data are available to show whether abiraterone acetate adding to hormone therapy is more effective than hormone therapy alone in patients with oligometastatic hormone-sensitive prostate cancer. However, unless objectives are limited in patients with oligometastasis, two randomised phase III trials, LATTITUDE[16] and STAMPEDE,[15] revealed the efficacy of abiraterone in addition to ADT for improving OS in patients with hormone-sensitive prostate cancer. LATTITUDE selected metastatic patients with "high-risk" clinicopathological features, defined as having at least two of the three following high-risk factors: a Gleason score of 8 or more,≥3 bone lesions and the presence of visceral metastasis. OS was significantly prolonged with the addition of abiraterone plus prednisone, compared with ADT alone (HR for death=0.62; 95% CI, 0.51 to 0.76; p<0.001).[16] In the STAMPEDE trial, heterogeneous metastatic (52%; 1002/1917 patients) and nonmetastatic (48%; 915/1917 patients) population were enrolled. OS was significantly longer in the abiraterone plus prednisolone group compared with the ADT alone group. The HR for death was 0.75 (95% CI, 0.48 to 1.18) in patients with nonmetastatic disease, and 0.61 (95% CI, 0.49 to 0.75) in those with metastatic disease.[15]

Both of the aforementioned trials potentially included patients with oligometastasis, such as patients with only three to five bone lesions, oligometastatic status was defined as maximum of three or five metastatic lesion in many studies, or solitary visceral metastasis plus a Gleason score ≥8. Although no information regarding the exact number of bone lesions and visceral metastases is available for the LATTITUDE trial, data stratified based on the volume of metastatic disease in the STAMPEDE trial were presented at European Society for Medical Oncology Congress 2018.[29] In all, 1002 of patients with metastasis enrolled in STAMPEDE trial was retrospectively stratified into low/high risk of LATITUDE criteria and low/high volume of CHAARTED criteria. OS was significantly prolonged with the addition of abiraterone plus prednisone, compared with ADT alone not only in high-risk population (HR for death=0.54; 95% CI, 0.41 to 0.70; p<0.001) but also low-risk population (HR for death=0.66; 95%, CI 0.44 to 0.96; p<0.041). When the CHAARTED criteria were used, same tendency was observed for OS (high-volume disease: HR for death=0.60; 95% CI, 0.46 to 0.78; p<0.001, low-volume disease: HR for death=0.64; 95% CI, 0.42 to 0.97; p<0.034).

We should be careful to interpret these results because of the post hoc retrospective analysis and subgroup analysis without sufficient power to evaluate OS. Under the presumption, these findings suggest that addition of abiraterone to ADT might be effective not only for the overall population but also for the low risk/volume or oligometastatic patients with metastatic hormone-sensitive prostate cancer.

CONCLUSIONS

A systemic therapy strategy including both hormone therapy and chemotherapy for oligometastatic prostate cancer has not yet been well established. ADT is the mainstay of current treatment for patients with metastatic prostate cancer, even in the oligometastatic state. Currently, promising data regarding MDT is emerging,[2 17] and multiple clinical trials are underway. The PEACE V trial (NCT03569241) is a prospective randomised, phase II trial that allocates MDT plus ADT with or without whole pelvic radiotherapy in patients with recurrent nodal oligometastatic hormone-sensitive prostate cancer. The ORIOLE trial (NCT02680587) is a randomised phase II trial evaluating the efficacy of SBRT compared with observation in patients with oligometastatic prostate cancer. However, there is currently no information available from large-sized, randomised phase III trials evaluating the efficacy of MDT with and without ADT in oligometastatic prostate cancer. Further investigation is warranted regarding whether MDT can shorten the duration of ADT, or eliminate the need for ADT entirely.

In terms of chemotherapy and new generation hormone therapy, some large-scale, randomised phase III trials in patients with metastatic hormone-sensitive prostate cancer overall have demonstrated survival benefits,[13–16] and some trials evaluating the addition of apalutamide (NCT02489318), enzalutamide (NCT02446405) and other drugs are ongoing. Subgroup data stratified by metastatic volume from these trials would provide useful information regarding treatment strategies for oligometastatic prostate cancer. We should be careful when selecting patients to receive chemotherapy or new generation hormone therapy in addition to ADT for oligometastatic prostate cancer. Continued investigation is required.

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